"Primary Abstract","Primary Paper","Secondary Abstract","Secondary Paper","Duplicate","Have PDF","Year","Author","Title","Journal","Issue","Id","DuplicateOf","Abstract","Primary Comment","Secondary Comment","Source","pmid","pub_date","pub_affiliation","pub_authorlang","pub_journal","pub_journalshort","pub_place","pub_type","pub_issn"
"Unknown","Unknown","Unknown","Unknown","","","2013","Alavanja, M. C. R., Ross, M. K., Bonner, M. R.","Reply to Increased cancer burden among pesticide applicators and others due to pesticide exposure","","63(5):366-367","996f5bbd-82a2-4239-9b14-e4c1c5eb1943","","","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Alavizadeh, S. H., Hosseinzadeh, H.","Bioactivity assessment and toxicity of crocin: A comprehensive review","","64:65-80","0acb5887-44ed-4e4b-accd-6e8c39a88f2b","","Since ancient times, saffron, the dried stigma of the plant Crocus sativus L. has been extensively used as a spice and food colorant; in folk medicine it has been reputed to be efficacious for the alleviation and treatment of ailments. In addition to the three founded major constituents including crocin, picrocrocin and safranal, presence of carotenoids, carbohydrates, proteins, anthocyanins, vitamins and minerals provide valuable insights into the health benefits and nutritional value of saffron. Of the carotenoids present in saffron, highly water-soluble crocin (mono and diglycosyl esters of a polyene dicarboxylic acid, named crocetin) is responsible for the majority of its color, and appears to possess various health-promoting properties, as an antioxidant, antitumor, memory enhancer, antidepressant, anxiolytic and aphrodisiac. It is also worth noting that the crocin principle of saffron exhibited high efficacy along with no major toxicity in experimental models. We would be remiss to not consider the great potential of saffron and crocin, which benefits the cuisine and health of human life throughout the world. The present study provides a comprehensive and updated report of empirical investigations on bioactivities and biological characteristics of crocin. Â© 2013 Elsevier Ltd.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2008","Aluigi, M. G., Angelini, C., Corte, G., Falugi, C.","The sea urchin, Paracentrotus lividus, embryo as a ""bioethical"" model for neurodevelopmental toxicity testing: effects of diazinon on the intracellular distribution of OTX2-like proteins","Cell biology and toxicology","24(6):587-601","c8310bb7-d686-470e-ab02-bc1913bee7ab","","Presently, a large effort is being made worldwide to increase the sustainability of industrial development, while preserving not only the quality of the environment but also that of animal and human life. In this work, sea urchin early developmental stages were used as a model to test the effects of the organophosphate pesticide (diazinon) on the regulation of gene expression by immunohistochemical localization of the human regulatory protein against the human OTX2. Egg exposure to diazinon did not affect fertilization; however, at concentrations 10(-5)-10(-6) M, it did cause developmental anomalies, among which was the dose-dependent alteration of the intracellular distribution of a regulatory protein that is immunologically related to the human OTX2. The severe anomalies and developmental delay observed after treatment at 10(-5) M concentration are indicators of systemic toxicity, while the results after treatment at 10(-6) M suggest a specific action of the neurotoxic compound. In this second case, exposure to diazinon caused partial delivery of the protein into the nuclei, a defective translocation that particularly affected the blastula and gastrula stages.

Therefore, the possibility that neurotoxic agents such as organophosphates may damage embryonic development is taken into account. Specifically, the compounds are known to alter cytoplasmic dynamics, which play a crucial role in regulating the distribution of intracellular structures and molecules, as well as transcription factors. Speculatively, basing our assumptions on Fura2 experiments, we submit the hypothesis that this effect may be due to altered calcium dynamics, which in turn alter cytoskeleton dynamics: the asters, in fact, appear strongly positive to the OTX2 immunoreaction, in both control and exposed samples. Coimmunoprecipitation experiments seem to supply evidence to the hypothesis.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Anadn, A., Valerio Jr, L. G.","Highlights of the XII International Congress on Toxicology, 19 23 July 2010, Barcelona, Spain","","6(11):1445-1450","83033006-b42b-493a-b934-3210aca8272f","","Importance of the field: There are few true international meetings dedicated to covering multiple areas of toxicology. The XII International Congress of Toxicology (IUTOX) held from 19 to 23 July 2010 in Barcelona, Spain is one such meeting. The IUTOX is important as its emphasis is on chemical safety and integrating approaches and alternative possibilities to protecting public health. The meeting was an important forum with professional interactions in different subspecialties of toxicology addressing these current topics. Areas covered in this review: The basis of toxic effects including mechanistic, effects testing, monitoring and alternative methods are covered in this meeting highlights article. Coverage of industry, clinical toxicologists, environmentalists, regulators and technological developers is provided. What the reader will gain: Insight into the coverage of topics discussed at the XII IUTOX meeting. Take home message: Current topics in toxicology with international impact are presently centered on new testing strategies, biomarkers and understanding mechanisms of toxicity to help address the safety and risk of substances relevant to public health. Â© 2010 Informa UK, Ltd.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Barry, K. H., Koutros, S., Berndt, S. I., Andreotti, G., Hoppin, J. A., Sandler, D. P., Burdette, L. A., Yeager, M., Freeman, L. E. B., Lubin, J. H., Ma, X., Zheng, T., Alavanja, M. C. R.","Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk","","119(12):1726-1732","1334a121-4435-4d25-850b-d771562a3539","","Background: Previous research indicates increased prostate cancer risk for pesticide applicators and pesticide manufacturing workers. Although underlying mechanisms are unknown, evidence suggests a role of oxidative DNA damage. Objectives: Because base excision repair (BER) is the predominant pathway involved in repairing oxidative damage, we evaluated interactions between 39 pesticides and 394 tag single-nucleotide polymorphisms (SNPs) for 31 BER genes among 776 prostate cancer cases and 1,444 male controls in a nested case-control study of white Agricultural Health Study (AHS) pesticide applicators. Methods: We used likelihood ratio tests from logistic regression models to determine p-values for interactions between three-level pesticide exposure variables (none/low/high) and SNPs (assuming a dominant model), and the false discovery rate (FDR) multiple comparison adjustment approach. Results: The interaction between fonofos and rs1983132 in NEIL3 [nei endonuclease VIII-like 3 (Escherichia coli)], which encodes a glycosylase that can initiate BER, was the most significant over-all [interaction p-value (pinteract) = 9.3 Ã- 10-6; FDR-adjusted p-value = 0.01]. Fonofos exposure was associated with a monotonic increase in prostate cancer risk among men with CT/TT genot{stroke}ypes for rs1983132 [odds ratios (95% confidence intervals)

for low and high use compared with no use were 1.65 (0.91, 3.01) and 3.25 (1.78, 5.92), respectively], whereas fonofos was not associated with prostate cancer risk among men with the CC genot{stroke}ype. Carbofuran and S-ethyl dipropylt{stroke}hiocarbamate (EPTC) interacted similarly with rs1983132; however, these interactions did not meet an FDR < 0.2. Conclusions: Our significant finding regarding fonofos is consistent with previous AHS findings of increased prostate cancer risk with fonofos exposure among those with a family history of prostate cancer. Although requiring replication, our findings suggest a role of BER genetic variation in pesticide-associated prostate cancer risk.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","1997","Bianchi-Santamaria, A., Gobbi, M., Cembran, M., Arnaboldi, A.","Human lymphocyte micronucleus genotoxicity test with mixtures of phytochemicals in environmental concentrations","Mutation research","388(1):27-32","04a242ae-0262-4881-ae45-785b9c6cc5bd","","This study was carried out to assess the genotoxicity of mixtures of pesticides using the micronucleus test with human lymphocytes in culture. Benomyl, azinphos-methyl, diazinon, dimethoate, pirimiphos-methyl pesticides were tested at doses estimated from their daily intake (EDI). Benomyl is a carbamate fungicide, the other compounds are organophosphorous insecticides. The compounds were tested both separately and in combination. The results showed a weak genotoxicity for three of the four organophosphorous insecticides and for benomyl. The various mixtures did not give additive effects.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2015","Boussabbeh, M., Ben Salem, I., Hamdi, M., Ben Fradj, S., Abid-Essefi, S., Bacha, H.","Diazinon, an organophosphate pesticide, induces oxidative stress and genotoxicity in cells deriving from large intestine","Environmental science and pollution research international","","e11e320b-6c08-431c-a400-e933386f524d","","Diazinon (DZ) (O,O-diethyl-O-[2-isopropyl-6-methyl-4-pyrimidinyl]phosphorothioate) is an organophosphate pesticide which is extensively used to control household insects and fruit and vegetable crops. The exposure to this pesticide has been linked to the development of the serious problem in several experimental animals. The contamination of food by DZ may increase its danger to humans. The aim of this study was to investigate the toxic effect of DZ on intestine using an in vitro model (HCT116). Therefore, we evaluated the cell viability, elucidated the generation of free radicals, measured the mitochondrial membrane potential, and valued DNA fragmentation. Our results showed that DZ is cytotoxic to HCT116. It causes oxidative damage through the generation of free radicals and induces lipid peroxidation and DNA fragmentation. We also demonstrated that such effects can be responsible for DZ-induced apoptosis.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2009","Buchanan, I., Liang, H. C., Khan, W., Liu, Z., Singh, R., Ikehata, K., Chelme-Ayala, P.","Pesticides and herbicides","","81(10):1731-1816","c7063c7d-c539-49a4-9a81-84bcbe90f0ef","","This is a review of literature published in 2008 that covered issues related to the presence of pesticides and herbicides in the environment. The review is divided into nine sections, including analytical methods, toxicology, monitoring, ecology, fate and transport, modeling, risk assessment, management and minimization, as well as treatment strategies. Copyright Â© 2009 Water Environment Federation.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2010","Buchanan, I., Liang, H. C., Liu, Z., Razaviarani, V., Rahman, Md Z.","Pesticides and herbicides","","82(10):1594-

1693","52d054d5-bbfb-40e1-b517-23abb5761fd8","","This is a review of literature published in 2009 that covered issues related to the presence of pesticides and herbicides in the environment. The review is divided into nine sections, including analytical methods, toxicology, monitoring, ecology, fate and transport, modeling, risk assessment, management and minimization, and treatment strategies. Copyright Â© 2010 Water Environment Federation.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2005","Cakir, S., Sarikaya, R.","Genotoxicity testing of some organophosphate insecticides in the Drosophila wing spot test","Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association","43(3):443-50","698fc4df-0a31-4469-a5b0-fbd2dad99904","","In this study, different concentrations of some organophosphate insecticides (methyl parathion, azamethiphos, dichlorvos and diazinon) have been evaluated for genotoxicity in the wing somatic mutation and recombination test (SMART) of Drosophila melanogaster. Third-instar larvae trans-heterozygous for two genetic markers mwh and flr, were treated at different concentrations (1 ppm, 3 ppm, 5 ppm, 7 ppm, 10 ppm) of the test compounds. A positive correlation was observed between total mutations and the number of wings having mutations. In addition, the observed mutations were classified according to size and type of mutation per wing. Chemicals used were ranked in decreasing order according to their genotoxic effects as diazinon, dichlorvos, methyl parathion, azamethiphos.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","1997","Campbell, P. M., Trott, J. F., Claudianos, C., Smyth, K. A., Russell, R. J., Oakeshott, J. G.","Biochemistry of esterases associated with organophosphate resistance in Lucilia cuprina with comparisons to putative orthologues in other Diptera","Biochemical genetics","35(1-2):17-40","51099e70-8f04-4399-a387-a9e4c22620c0","","Esterase activities associated with organophosphate insecticide resistance in the Australian sheep blowfly, Lucilia cuprina, are compared with similar activities in other Diptera. The enzymes making the major contribution to methyl butyrate hydrolysis (""ali-esterase"") in L. cuprina, M. domestica, and D. melanogaster comigrate during electrophoresis. The enzymes in L. cuprina and D. melanogaster correspond to the naphthyl acetate hydrolyzing E3 and EST23 isozymes of those species. These and previously published data suggest that the ali-esterases of all three species are orthologous. Strains of L. cuprina fall into four groups on the basis of quantitative determinations of their ali-estesterase, OP hydrolase, and malathion carboxylesterase activities and these groups correspond to their status with respect to two types of OP resistance. Strains susceptible to OP's have high ali-esterase, low OP hydrolase, and intermediate MCE activities; those resistant to malathion but not diazinon have low ali-esterase, intermediate OP hydrolase, and high MCE activities; those resistant to diazinon but not malathion have low ali-esterase, high OP hydrolase, and low MCE activities; those resistant to both OPs have low ali-esterase, high OP hydrolase, and high MCE activities. The correlated changes among the three biochemical and two resistance phenotypes suggest that they are all properties of one gene/enzyme system; three major allelic variants of that system explain OP susceptibility and the two types of OP resistance. Models are proposed to explain the joint contribution of OP hydrolase and MCE activities to malathion resistance and the invariant association of low ali-esterase and elevated OP hydrolase activities in either type of resistance.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","1999","Claudianos, C., Russell, R. J., Oakeshott, J. G.","The same amino acid substitution in orthologous esterases confers

organophosphate resistance on the house fly and a blowfly","Insect biochemistry and molecular biology","29(8):675-86","8d588735-8426-4c4e-9d0c-cfad96efffbe","","Organophosphate (OP) insecticide resistance in certain strains of Musca domestica is associated with reduction in the carboxylesterase activity of a particular esterase isozyme. This has been attributed to a 'mutant ali-esterase hypothesis', which invokes a structural mutation to an ali-esterase resulting in the loss of its carboxylesterase activity but acquisition of OP hydrolase activity. It has been shown that the mutation in Lucilia cuprina is a Gly137-->Asp substitution in the active site of an esterase encoded by the Lc alpha E7 gene (Newcomb, R.D., Campbell, P.M., Ollis, D.L., Cheah, E., Russell, R.J., Oakeshott, J.G., 1997. A single amino acid substitution converts a carboxylesterase to an organophosphate hydrolase and confers insecticide resistance on a blowfly. Proc. Natl. Acad. Sci. USA 94, 7464-7468). We now report the cloning and characterisation of the orthologous M. domestica Md alpha E7 gene, including the sequencing of cDNAs from the OP resistant Rutgers and OP susceptible sbo and WHO strains. The Md alpha E7 gene has the same intron structure as Lc alpha E7 and encodes a protein with 76% amino acid identity to Lc alpha E7. Comparisons between susceptible and resistance alleles show resistance in M. domestica is associated with the same Gly137-->Asp mutation as in L. cuprina. Bacterial expression of the Rutgers allele shows its product has OP hydrolase activity. The data indicate identical catalytic mechanisms have evolved in orthologous Md alpha E7 and Lc alpha E7 molecules to endow diazinon-type resistance on the two species of higher Diptera.","","","RefMan","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2010","ÄŒoloviÄ‡, M., KrstiÄ‡, D., PetroviÄ‡, S., Leskovac, A., JoksiÄ‡, G., SaviÄ‡, J., Franko, M., TrebÅ¡e, P., VasiÄ‡, V.","Toxic effects of diazinon and its photodegradation products","","193(1):9-18","a564c064-dc47-481a-81dd-f7b433b66bdd","","The toxic effects of diazinon and its irradiated solutions were investigated using cultivated human blood cells (lymphocytes and erythrocytes) and skin fibroblasts. Ultra Performance Liquid Chromatography (UPLC)-UV/VIS system was used to monitor the disappearance of starting diazinon during 115-min photodegradation and formation of its by-products (diazoxon and 2-isopropyl-6-methyl-4-pyrimidinol (IMP)) as a function of time. Dose-dependent AChE and Na+/K+-ATPase inhibition by diazinon was obtained for all investigated cells. Calculated IC50 (72 h) values, in M, were: 7.5 Ã- 10-6/3.4 Ã- 10-5, 8.7 Ã- 10-5/6.6 Ã- 10-5, and 3.0 Ã- 10-5/4.6 Ã- 10-5 for fibroblast, erythrocyte and lymphocyte AChE/Na+/K+-ATPase, respectively. Results obtained for reference commercially purified target enzymes indicate similar sensitivity of AChE towards diazinon (IC50 (20 min)-7.8 Ã- 10-5M), while diazinon concentrations below 10 mM did not noticeably affect Na+/K+-ATPase activity. Besides, diazinon and IMP induced increasing incidence of micronuclei (via clastogenic mode of action) in a dose-dependent manner up to 2 Ã- 10-6 M and significant inhibition of cell proliferation and increased level of malondialdehyde at all investigated concentrations. Although after 15-min diazinon irradiation formed products do not affect purified commercial enzymes activities, inhibitory effect of irradiated solutions on cell enzymes increased as a function of time exposure to UV light and resulted in significant reduction of AChE (up to 28-45%) and Na+/K+-ATPase (up to 35-40%) at the end of irradiation period. Moreover, photodegradation treatment strengthened prooxidative properties of diazinon as well as its potency to induce cytogenetic damage. Â© 2009 Elsevier Ireland Ltd. All rights reserved.","","","RefMan","","","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2004","Conners, D. E., Black, M. C.","Evaluation of lethality and genotoxicity in the freshwater mussel Utterbackia imbecillis (Bivalvia: Unionidae) exposed singly and in combination to chemicals used in lawn care","Archives of environmental contamination and toxicology","46(3):362-71","a02df837-7f8a-4926-ad34-4854f9699c2a","","Many chemicals, including fertilizers, herbicides, and insecticides, are routinely applied to turf in the care and maintenance of lawns. These chemicals have the potential to leach into nearby surface waters and adversely affect aquatic biota. In this study, we evaluated the lethal and genotoxic effects of chemicals used in lawn care on an early life stage of freshwater mussels (Utterbackia imbecillis). The chemicals tested were copper and commercial formulations of atrazine, glyphosate, carbaryl, and diazinon. Mussel glochidia were exposed to chemicals singly or in combination (equitoxic and environmentally realistic mixtures) for 24 h and toxic interactions were evaluated with Marking's additive index. Genotoxicity was quantified with the alkaline single-cell gel electrophoresis assay (Comet assay). In acute tests, copper was the most toxic of all chemicals evaluated (LC50 = 37.4 microg/L) and carbaryl was the most toxic of all pesticides evaluated (LC50 = 7.9 mg/L). In comparison to other aquatic organisms commonly used in toxicity tests (e.g., amphipods, cladocerans, and chironomids), mussel glochidia were as or more sensitive to the chemicals evaluated with the exception of diazinon, where mussels were observed to be less sensitive. The combined toxicity of equitoxic and environmentally realistic mixtures to mussels was additive. Genotoxic responses were observed in mussels exposed to copper, atrazine and diazinon at levels below their respective no-observed-effect concentrations. Together, these data indicate that freshwater mussels are among the most sensitive aquatic organisms tested for some chemicals commonly used in lawn care and that DNA damage may be useful as a screening tool to evaluate potential sublethal effects of lawn care products on non-target aquatic organisms.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2012","D'Agostino, J., Zhang, H., Kenaan, C., Hollenberg, P.","Mechanism-based inactivation of human cytochrome P450 2B6 by chlorpyrifos and related organophosphate pesticides","","44:33","bfdab149-3ae8-46a3-b7fb-15c2de29df85","","Chlorpyrifos (CPS) is a commonly used organophosphate pesticide which is bioactivated by P450s to give the toxic metabolite chlorpyrifos-oxon (CPO). This reaction also results in the release of sulfur, which is implicated in mechanismbased inactivation (MBI) of P450s. CYP2B6 was determined to have the greatest catalytic efficiency for CPO formation in vitro, therefore we set out to characterize the MBI of CYP2B6 by CPS. CPS inactivated CYP2B6 in a time- and concentration-dependent manner with a kinact of 1.97 min-1, a Ki of 0.47 Î¼M, and a partition ratio of 17.7. The rate of CPO formation and the rate of the first electron transfer from cytochrome P450 reductase to CYP2B6 in the presence of CPS were determined and the values were supportive of the rapid inactivation observed. We further evaluated the ability of the organophosphate pesticides chlorpyrifos-methyl, diazinon, parathion-methyl, malathion, and azinophos-methyl to inactivate CYP2B6. These organophosphate pesticides were also potent MBIs of CYP2B6 characterized by similar kinact and ki values. The inactivation of CYP2B6 by CPS was accompanied by loss of P450 detectable by its CO reduced spectra and, to a lesser extent, loss of detectable heme. High molecular weight adducts were observed when inactivated CYP2B6 was run on SDS-PAGE gels indicating protein aggregation. We further explored the ability of CPS to inactivate CYP2B1 and CYP2B4, as well as CYP2B6 with mutation of the cysteines at positions 152 or

475 to serine. The results of IC50 shift experiments revealed that only CYP2B6 was inactivated and the inactivation was unaffected by mutation of cysteine to serine at positions 152 and 475. These results indicate that CPS and other organophosphate pesticides are potent MBIs of CYP2B6, which may have implications in the toxicity of these pesticides as well as potential pesticide-drug interactions.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2015","D'Agostino, J., Zhang, H., Kenaan, C., Hollenberg, P. F.","Mechanism-Based Inactivation of Human Cytochrome P450 2B6 by Chlorpyrifos","","28(7):1484-1495","24cfe922-edad-47bd-b3fb-7eccd282f74a","","(Graph Presented) Chlorpyrifos (CPS) is a commonly used pesticide which is metabolized by P450s into the toxic metabolite chlorpyrifos-oxon (CPO). Metabolism also results in the release of sulfur, which has been suggested to be involved in mechanism-based inactivation (MBI) of P450s. CYP2B6 was previously determined to have the greatest catalytic efficiency for CPO formation in vitro. Therefore, we characterized the MBI of CYP2B6 by CPS. CPS inactivated CYP2B6 in a time- and concentration-dependent manner with a k<inf>inact</inf> of 1.97 min⁻¹, a K<inf>I</inf> of 0.47 Î¼M, and a partition ratio of 17.7. We further evaluated the ability of other organophosphate pesticides including chorpyrifos-methyl, diazinon, parathion-methyl, and azinophos-methyl to inactivate CYP2B6. These organophosphate pesticides were also potent MBIs of CYP2B6 characterized by similar k<inf>inact</inf> and K<inf>I</inf> values. The inactivation of CYP2B6 by CPS was accompanied by the loss of P450 detectable in the CO reduced spectrum and loss of detectable heme. High molecular weight aggregates were observed when inactivated CYP2B6 was run on SDS-PAGE gels indicating protein aggregation. Interestingly, we found that the rat homologue of CYP2B6, CYP2B1, was not inactivated by CPS despite forming CPO to a similar extent. On the basis of the locations of the Cys residues in the two proteins which could react with released sulfur during the metabolism of CPS, we investigated whether the C475 in CYP2B6, which is not conserved in CYP2B1, was the critical residue for inactivation by mutating it to a Ser. CYP2B6 C475S was inactivated to a similar extent as wild type CYP2B6 indicating that C475 is not likely the key difference between CYP2B1 and CYP2B6 with respect to inactivation. These results indicate that CPS and other organophosphate pesticides are potent MBIs of CYP2B6 which may have implications for the toxicity of these pesticides as well as the potential for pesticide-drug interactions.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2013","Dalzell, A., Glass, R.","Extrapolation of toxicology endpoint data in developing integrated human and environmental risk assessments","","221:S221","2f9a62cb-3eab-4899-99ed-03f7df1b79c8","","Risk assessments for human and environmental exposure to chemicals tend to be done as separate procedures, although both approaches face similar limitations. With the development of cumulative and aggregate exposure modelling, the FP7 project â€œHEROICâ€? aims to establish and co-ordinate a global network of experts and stakeholders to establish stronger interfaces between human and environmental disciplines leading to unambiguous integrated risk assessment (IRA) procedures. Toxicological endpoints used in risk assessment (RA) often differ significantly between mammalian toxicology and ecotoxicology, although some overlap exists, which could lead to the establishment of IRA. Case studies are being performed which examine endpoints for human and environmental hazard assessment, and possibilities for cross discipline approaches leading to more robust and cost effective IRA procedures. One of the case

studies being undertaken to investigate such a use of data addresses the compounds cypermethrin, deltamethrin, diazinon and imazalil. They are often assessed by different regulatory authorities, being used as plant protection products and veterinary medicines. Endpoints for these compounds identified in the open literature include growth, motility and survival of aquatic invertebrates and algae, biomarkers of oxidative stress, and changes in neuronal metabolism (e.g. acetylcholinesterase activity). Of particular interest is the micronucleus test, an easily quantifiable assay of chromosome and genome mutations applicable to species of ecotoxicological relevance (plants, fish) and also to mammals, as it can be performed on cells after in vivo exposure as well as directly in vitro. Neurodevelopmental toxicity data available from zebrafish could be another useful endpoint to explore.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2005","D'Amelio, M., Ricci, I., Sacco, R., Liu, X., D'Agruma, L., Muscarella, L. A., Guarnieri, V., Militerni, R., Bravaccio, C., Elia, M., Schneider, C., Melmed, R., Trillo, S., Pascucci, T., Puglisi-Allegra, S., Reichelt, K. L., Macciardi, F., Holden, J. J., Persico, A. M.","Paraoxonase gene variants are associated with autism in North America, but not in Italy: possible regional specificity in gene-environment interactions","Molecular psychiatry","10(11):1006-16","bd413ff3-504a-40ab-be01-2a1b10a4cbe2","","Organophosphates (OPs) are routinely used as pesticides in agriculture and as insecticides within the household. Our prior work on Reelin and APOE delineated a gene-environment interactive model of autism pathogenesis, whereby genetically vulnerable individuals prenatally exposed to OPs during critical periods in neurodevelopment could undergo altered neuronal migration, resulting in an autistic syndrome. Since household use of OPs is far greater in the USA than in Italy, this model was predicted to hold validity in North America, but not in Europe. Here, we indirectly test this hypothesis by assessing linkage/association between autism and variants of the paraoxonase gene (PON1) encoding paraoxonase, the enzyme responsible for OP detoxification. Three functional single nucleotide polymorphisms, PON1 C-108T, L55M, and Q192R, were assessed in 177 Italian and 107 Caucasian-American complete trios with primary autistic probands. As predicted, Caucasian-American and not Italian families display a significant association between autism and PON1 variants less active in vitro on the OP diazinon (R192), according to case-control contrasts (Q192R: chi2=6.33, 1 df, P<0.025), transmission/disequilibrium tests (Q192R: TDT chi2=5.26, 1 df, P<0.025), family-based association tests (Q192R and L55M: FBAT Z=2.291 and 2.435 respectively, P<0.025), and haplotype-based association tests (L55/R192: HBAT Z=2.430, P<0.025). These results are consistent with our model and provide further support for the hypothesis that concurrent genetic vulnerability and environmental OP exposure may possibly contribute to autism pathogenesis in a sizable subgroup of North American individuals.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2015","Daniela A, P., Jasmine, S., Yichang, C., Patrick, A.","Reproductive toxicity and meiotic dysfunction following exposure to the pesticides Maneb, Diazinon and Fenarimol","","4(3):645-654","540cb324-4bb3-4210-9d68-998a9e737e54","","The comprehensive identification and mechanistic analysis of reproductive toxicants constitutes one of the major hurdles in the toxicological assessment of chemicals originating from the large number of chemicals to be tested and the difficulty in examining germ cells at various stages of their development. We previously described the development of an assay in the roundworm

Caenorhabditis elegans that allows the detection of chemicals bearing aneugenic activity and that could be used for the detection of germline toxicity. We present here new evidence for the reproductive toxicity of three pesticides identified in our germline toxicity assay: Maneb, Diazinon and Fenarimol. We show that all three pesticides cause an acute germline nuclear loss in exposed nematodes in a dose-dependent fashion. The loss of germline nuclei coincides with the meiotic stage of pachytene during Prophase I and is dependent on the germline apoptotic machinery suggesting activation of a meiotic checkpoint. Further investigation revealed a profound dysregulation of the meiotic program as evidenced by (1) an alteration of the kinetics of double strand repair, (2) the disruption of the process of chromosome morphogenesis at the end of Prophase I and (3) the reorganization of the meiotic differentiation gradient inherent to the C. elegans germline following exposure to Maneb and Diazinon. These defects correlate with a significant increase in embryonic lethality and a corresponding decrease in the number of progeny. These results therefore provide strong evidence for the reproductive toxicity of Maneb, Diazinon and Fenarimol rooted in the alteration of early steps of germ cell differentiation.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","1996","Davies, A. G., Game, A. Y., Chen, Z., Williams, T. J., Goodall, S., Yen, J. L., McKenzie, J. A., Batterham, P.","Scalloped wings is the Lucilia cuprina Notch homologue and a candidate for the modifier of fitness and asymmetry of diazinon resistance","Genetics","143(3):1321-37","98671a52-0827-4db3-ab68-4c22cee2d044","","The Scalloped wings (Scl) gene of the Australian sheep blowfly, Lucilia cuprina, is shown to be the homologue of the Drosophila melanogaster Notch gene by comparison at the DNA sequence and genetic levels. A L. cuprina genomic fragment, which shows strong identity with the Notch (N) gene at the molecular level, hybridizes to the location of the Scl gene on polytene chromosomes. The two genes are functionally homologous; the dominant and recessive Notch-like phenotypes produced by mutations in the Scl gene allow these alleles to be classed as N-like or Abruptex-like. The Scl gene is under investigation as a candidate for the fitness and asymmetry Modifier (M) of diazinon resistance. We show that M affects the penetrance of wing and bristle phenotypes associated with two Scl alleles in a manner consistent with the M being an allele of Scl. In addition, we report a phenotypic interaction between the diazinon-resistance mutation, Rop-1, and the same alleles of Scl. We propose that the product of Rop-1, an esterase, may be involved in cell adhesion in developmental processes involving the Scl gene product.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Deferme, L., Wolters, J., Claessen, S., Briede, J., Kleinjans, J.","Oxidative Stress Mechanisms Do Not Discriminate between Genotoxic and Nongenotoxic Liver Carcinogens","Chemical research in toxicology","28(8):1636-46","f0ef2160-0e41-4616-9584-c3a363e0f08f","","It is widely accepted that in chemical carcinogenesis different modes-of-action exist, e.g., genotoxic (GTX) versus nongenotoxic (NGTX) carcinogenesis. In this context, it has been suggested that oxidative stress response pathways are typical for NGTX carcinogenesis. To evaluate this, we examined oxidative stress-related changes in gene expression, cell cycle distribution, and (oxidative) DNA damage in human hepatoma cells (HepG2) exposed to GTX-, NGTX-, and noncarcinogens, at multiple time points (4-8-24-48-72 h). Two GTX (azathriopine (AZA) and furan) and two NGTX (tetradecanoyl-phorbol-acetate, (TPA) and tetrachloroethylene (TCE)) carcinogens as well as two noncarcinogens (diazinon (DZN, d-

mannitol (Dman)) were selected, while per class one compound was deemed to induce oxidative stress and the other not. Oxidative stressors AZA, TPA, and DZN induced a 10-fold higher number of gene expression changes over time compared to those of furan, TCE, or Dman treatment. Genes commonly expressed among AZA, TPA, and DZN were specifically involved in oxidative stress, DNA damage, and immune responses. However, differences in gene expression between GTX and NGTX carcinogens did not correlate to oxidative stress or DNA damage but could instead be assigned to compound-specific characteristics. This conclusion was underlined by results from functional readouts on ROS formation and (oxidative) DNA damage. Therefore, oxidative stress may represent the underlying cause for increased risk of liver toxicity and even carcinogenesis; however, it does not discriminate between GTX and NGTX
carcinogens.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Di Giorgio, C., Liu, W., Sarrazin, L., Wafo, E., Moreau, X., De Jong, L., Thiery, A., De Meo, M.","Organic pollution and genotoxicity of sediments of the Palun marshes (Berre lagoon, France)","Journal of environmental quality","39(2):558-67","cf793c20-72fd-493c-9ece-49e5b01d1741","","The impact of industrial, rural, and urban activities on two runnels (B1, B2, and B3 from Beausset runnel and V1 and V2 from Vallat du Ceinturon runnel) located in the Palun marshes (Berre lagoon, France) was evaluated by analyzing 16 polycyclic aromatic hydrocarbons (PAHs), 1-nitropyrene (1-NP), 1-aminopyrene (1-AP), and six pesticides in sediment samples. The mutagenicity was assessed with the Salmonella mutagenicity test using tester strains TA98+S9 Mix and YG1041 +/- S9 Mix. The clastogenicity was evaluated with the micronucleus assay on Chinese Ovarian cells +/- S9 Mix. A gradient of PAHs concentrations was observed from B1 (3359 microg kg(-1) dry weight [dw]), close to industrial zones, to V2 (497 microg kg(-1) dw), away from the source of pollution. Similar gradient was noted for 1-AP (from B1: 11.8 microg kg(-1) dw to V2: 0.6 microg kg(-1) dw). However, this trend was not observed in 1-NP concentrations (concentrations ranged from 1.2 microg kg(-1) dw [V1] to 0.4 microg kg(-1) dw [B1]). Pesticides were detected in all samples. Diazinon and dieldrin were found in high concentrations in B1 extracts (74.5 and 39.9 microg.kg(-1) dw, respectively). All the sediments except V2 were mutagenic with strain TA98+S9 Mix. The mutagenicity was linked to the presence of PAHs (V1), nitroarenes (B1 and B3) and aromatic amines (B2). All sediments were clastogenic with and without S9 Mix except V1 extract, which was negative without S9 Mix. Overall, the two runnels in the Palun marshes were found to be polluted by many organic compounds that originate from direct human activities and pose a significant genotoxic risk.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2016","Ezzi, L., Haouas, Z., Salah, I. B., Sakly, A., Grissa, I., Chakroun, S., Kerkeni, E., Hassine, M., Mehdi, M., Cheikh, H. B.","Toxicopathic changes and genotoxic effects in liver of rat following exposure to diazinon","Environmental science and pollution research international","","a2c40856-b2aa-4aae-996a-930cc4e547e4","","In general, people may come in contact with mixtures of insecticides through domestic use, consumption of contaminated food or drinks, and/or living close to treated areas. We analyzed the toxic effects of diazinon on histological structure of liver and hematological parameters in male rats. DNA-damaging potential of diazinon was also investigated using the comet assay in blood cells and the micronucleus test in bone marrow. Two groups of six male rats orally received different amounts of diazinon: 1/50 and 1/25 LD 50 for 4 weeks (5 day/week). The present study showed that diazinon caused hypertrophy of sinusoids, central vein, and

portal triad, in addition to the formation of oedema, vacuoles, hemorrhage, necrosis, and lymphoid infiltration in rats' liver. A significant decrease in red blood cells, hemoglobin, hematocrite levels, and platelet counts was observed in the treated groups. However, the white blood cell count increased. Micronucleus test results revealed aneugenic effects of diazinon. Furthermore, we noticed an increase in comet tail length in treated groups. So, the comet assay confirmed the genotoxic potential of diazinon in vivo. On the assumption that all alterations observed in rats could be observed in human, it is necessary to raise the awareness about the health risk posed by this insecticide.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Fan, F., You, Z., Li, Z., Cheng, J., Tang, Y., Tang, Z.","A butterfly effect: Highly insecticidal resistance caused by only a conservative residue mutated of drosophila melanogaster acetylcholinesterase","","15(10):1229-1236","96a19cf0-577f-4c71-ab2e-9e9bb4435221","","Acetylcholinesterase (AChE) and its mutation recently emerged as a significant research area, due to its resistance against organophosphate and carbamate insecticides. Residue G265, which is always a conservative residue, mutated to A265 is the most frequent mutant of AChE in Drosophila populations. However, only this mutation caused a ""butterfly effect"" that gives high insecticidal resistance. Herein, the models of sensitive strain (Dm-S) and the resistance strain (Dm-R) were constructed, to give a total of 2000 ps molecular dynamics simulation and to reveal the insecticidal resistance mechanism, with implied, the active gorge of Dm-R was much less flexible than that of Dm-S. The ""back door"" channel was widened to accelerate the detoxication against insecticides by the conformation changing of W83 and I161. All the distances (S238-H480, S238-G150, S238-G151, Y71-M153) in Dm-R became smaller than those in Dm-S, which may deeply influence the binding between the insecticides and DmAChE. Â© Springer-Verlag 2009.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2005","Foil, L. D., Guerrero, F., Alison, M. W., Kimball, M. D.","Association of the kdr and superkdr sodium channel mutations with resistance to pyrethroids in Louisiana populations of the horn fly, Haematobia irritans irritans (L.)","Veterinary parasitology","129(1-2):149-58","c83d7467-a261-471b-a92f-1679f3439e1f","","Pyrethroid resistance in three horn fly populations in Louisiana was monitored by weekly fly counts, filter paper bioassays, and diagnostic PCR assays for the presence of pyrethroid resistance-associated mutations in the sodium channel gene coding region. The PCR assay for the knockdown resistance (kdr) and superkdr sodium channel mutations was used to determine the frequency of the target site insensitivity mechanism in the populations of horn flies, which possessed varying degrees of insecticide resistance. The bioassays and frequency of homozygous-resistant (RR) kdr genotypes were relative predictors of the fly control subsequently observed. Flies exposed to filter paper impregnated with a discriminating concentration of one of four different insecticides were collected when 50% mortality was estimated. Genotypes for the dead flies and the survivors were determined by the PCR assay. The results of the PCR assays indicated that the genotype at the kdr locus of the flies exposed to the two pyrethroids had an effect upon whether the flies were considered to be alive or dead at the time of collection. The kdr genotype of flies exposed to either diazinon or doramectin was unrelated to whether the flies were considered to be alive or dead, except for a single comparison of flies exposed to diazinon. When possible interactions of the kdr and superkdr mutations were compared, we found that there were no associations with the response to diazinon and doramectin.

For one location, there were no survivors of the 75 flies with the SS-SS (superkdr-kdr) homozygous susceptible wild type genotype exposed to pyrethroids, while there were survivors in all of the other five genotypes. The SS-RR genotype flies were more susceptible to the pyrethroids than the SR-RR flies, but that was not the case for exposure to diazinon or doramectin. In the St. Joseph population, there were an adequate number of flies to demonstrate that the SS-SR genotype was more susceptible to pyrethroids than the SS-RR and that flies with the SR-SR genotype were more susceptible to pyrethroids than the flies with the SR-RR genotype.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","1996","Frolichsthal, P., Piatti, E.","[Evaluation of micronuclei in primary hepatocyte culture in rats treated with organophosphoric compounds]","Bollettino chimico farmaceutico","135(9):541-5","71a34188-b268-45f3-a6f8-28fadaafae64","","We have evaluated the genotoxic effect of the three organophosphorous (OPs) insecticides dimethoate (DIM), azinphosmethyl (AZN) and diazinon (DIA) or in combination, at a ratio frequently found in foodstuffs by residual analysis. We have carried out the micronucleus (MN) test on cultured rat hepatocytes which were induced to proliferate by epidermal growth factor (EGF), and treated with the insecticides for 48 hours. The doses tested were chosen on the basis of cytotoxicity tests such as Trypan Blue exclusion and mitotic index inhibition. The results showed that AZN was the most toxic and DIM the least toxic compound. None of the compounds tested showed a genotoxic effect when examined separately. Conversely, a significant increase in MN frequency was observed when the three OPs were used in combination at the lowest concentration used when each compound was tested alone.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2000","Furlong, C. E., Li, W. F., Brophy, V. H., Jarvik, G. P., Richter, R. J., Shih, D. M., Lusis, A. J., Costa, L. G.","The PON1 gene and detoxication","Neurotoxicology","21(4):581-7","32e30950-8380-4e3e-86a0-a5ce0778c233","","It has been assumed since its discovery that serum paraoxonase (PON1) plays a major role in the detoxication of specific organophosphorus compounds. It was also assumed that individuals with low PON1 activity would be more susceptible to paraoxon/parathion poisoning than individuals with higher PON1 activity. Evidence supporting this hypothesis was provided by injection of rabbit PON1 into rodents. Injected PON1 protected against paraoxon toxicity in rats and chlorpyrifos oxon toxicity in mice. The recent availability of PON1 knockout mice has provided an in vivo system with which one can more closely examine the role of PON1 in detoxication. PON1 knockout mice demonstrated dramatically increased sensitivity to chlorpyrifos oxon and diazoxon and moderately increased sensitivity to the respective parent compounds. The PON1 knockout mutation also resulted in the elimination of liver PON1 activity, accounting for the dramatic increase in sensitivity to chlorpyrifos oxon and diazoxon. Totally unexpected was our finding that the PON1 knockout mice were not more sensitive to paraoxon. This was particularly surprising in light of the earlier enzyme injection experiments. Differences in the relative catalytic efficiencies of rabbit vs. mouse PON1 for the specific oxon forms explain these observations. Mouse PON1 has good catalytic efficiency for the hydrolysis of diazoxon and chlorpyrifos oxon, but a poor efficiency for paraoxon hydrolysis relative to rabbit PON1. The human PON1Q192 isoform has a catalytic efficiency similar to that of mice, whereas the human PON1R192 isoform has a much better catalytic efficiency, predicting that individuals expressing high levels of the PONIR192 isoform may have increased resistance to paraoxon

toxicity.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Ghosh, S., Kumar, R., Nagar, G., Kumar, S., Sharma, A. K., Srivastava, A., Kumar, S., Ajith Kumar, K. G., Saravanan, B. C.","Survey of acaricides resistance status of Rhipiciphalus (Boophilus) microplus collected from selected places of Bihar, an eastern state of India","","6(5):668-675","a8f80aa8-224b-4626-8833-e677206048f4","","Monitoring acaricide resistance in field ticks and use of suitable managemental practices are essential for controlling tick populations infesting animals. In the present study, the acaricide resistance status in Rhipicephalus (Boophilus) microplus ticks infesting cattle and buffaloes of five districts located in the eastern Indian state, Bihar were characterized using three data sets (AIT, Biochemical assays and gene sequences). Adult immersion test (AIT) was adopted using seven field isolates and their resistance factor (RF) was determined. Six isolates (DNP, MUZ, BEG, VSH, DRB and SUL) were found resistant to both deltamethrin and diazinon and except VSH all were resistant to cypermethrin. One isolate (PTN) was susceptible with a RF below 1.5. To understand the possible mode of resistance development, targeted enzymes and gene sequences of the para sodium channel and achetylcholinesterase 2 (AChE2) were analyzed. The esterase, monooxygenase and glutathione-S-transferase (GST) activity of reference susceptible IVRI-I line was determined as 2.47 Â± 0.007. nmol/min/mg protein, 0.089 Â± 0.0016. nmol/mg of protein and 0.0439 Â± 0.0003. nmol/mg/min respectively, which increased significantly in the resistant field isolates. However, except esterases, the fold increase of monooxygenase (1.14-2.27 times) and GST (0.82-1.53 times) activities were not very high. A cytosine (C) to adenine (A) nucleotide substitution (CTC to ATC) at position 190 in domain II S4-5 linker region was detected only in one isolate (SUL) having RF of 34.9 and in the reference deltamethrin resistant line (IVRI-IV). However, the T2134A mutation was not detected in domain IIIS6 transmembrane segment of resistant isolates and also in reference IVRI-IV line despite of varying degree of resistance. The flumethrin specific G215T and the recently identified T170C mutations were also absent in domain II sequences under study. Four novel amino acid substitutions in AChE2 gene of field isolates and in organophosphate (OP) resistant reference IVRI-III line were identified which can possibly have a role in resistance development.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Girgis, S. M.","Potential protective effects of vitamin E on diazinon-induced DNA damage and some haematological and biochemical alterations in rats","","205:S230","0e191d48-28cd-4730-ade3-378aabede7e1","","Purpose: Diazinon (DZN), is a commonly used organophosphorous (OP) pesticide to control a variety of insects in agriculture and in the environment. Vitamin E is a primary antioxidant that plays an important role in protecting cells against toxicity by inactivating free radicals generated following pesticides exposure. Methods: The possible protective effect of vitamin E against DZN-induced adverse effects on haematological and biochemical indices and on genotoxicity using comet assay and micronucleus test for measuring the DNA damage was studied. The tissue DZN residues in liver, kidney and muscle of the rats were determined. Results of the study: DZN administration significantly decreased Hb concentration, RBC count and PCV values. Meanwhile, a significant increase in WBCs, ALT, AST and total cholesterol was detected. However, vitamin E supplementation together with DZN improves these alterations. DZN residue level is highest in the kidney than that in liver and muscle tissues. Vitamin E together with DZN reduces the residual values in the tissues. A significant increase in

tail length of comets as well in the frequency of micronucleated cells (MNCs) following DZN administration was achieved. Co-administrated vitamin E with DZN resulted in decrease in tail length of comets and the percentage of MNCs compared to DZN alone. Vitamin E, on the other hand, was observed to repair the genotoxicity and improves the haematological and biochemical changes induced by DZN. It can be concluded that vitamin E has protective effect against DZN effects and supplementation of vitamin E might be beneficial to DZN exposed populations.","","","RefMan","","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2015","Goodson, W. H., Lowe, L., Carpenter, D. O., Gilbertson, M., Ali, A. M., de Cerain Salsamendi, A. L., Lasfar, A., Carnero, A., Azqueta, A., Amedei, A., Charles, A. K., Collins, A. R., Ward, A., Salzberg, A. C., Colacci, A. M., Olsen, A. K., Berg, A., Barclay, B. J., Zhou, B. P., Blanco-Aparicio, C., Baglole, C. J., Dong, C., Mondello, C., Hsu, C. W., Naus, C. C., Yedjou, C., Curran, C. S., Laird, D. W., Koch, D. C., Carlin, D. J., Felsher, D. W., Roy, D., Brown, D. G., Ratovitski, E., Ryan, E. P., Corsini, E., Rojas, E., Moon, E. Y., Laconi, E., Marongiu, F., Al-Mulla, F., Chiaradonna, F., Darroudi, F., Martin, F. L., Van Schooten, F. J., Goldberg, G. S., Wagemaker, G., Nangami, G. N., Calaf, G. N., Williams, G. P., Wolf, G. T., Koppen, G., Brunborg, G., Kim Lyerly, H., Krishnan, H., Hamid, H. A., Yasaei, H., Sone, H., Kondoh, H., Salem, H. K., Hsu, H. Y., Park, H. H., Koturbash, I., Miousse, I. R., Ivana Scovassi, A., Klaunig, J. E., VondrÃ¡Ä?ek, J., Raju, J., Roman, J., Wise, J. P., Whitfield, J. R., Woodrick, J., Christopher, J. A., Ochieng, J., Martinez-Leal, J. F., Weisz, J., Kravchenko, J., Sun, J., Prudhomme, K. P., Narayanan, K. B., Cohen-Solal, K. A., Moorwood, K., Gonzalez, L., Soucek, L., Jian, L., D'Abronzo, L. S., Lin, L. T., Li, L., Gulliver, L., McCawley, L. J., Memeo, L., Vermeulen, L., Leyns, L., Zhang, L., Valverde, M., Khatami, M., Romano, M. F., Chapellier, M., Williams, M. A., Wade, M., Manjili, M. H., Lleonart, M. E., Xia, M., Guzman, M. J. G., Karamouzis, M. V., Kirsch-Volders, M., Vaccari, M., Kuemmerle, N. B., Singh, N., Cruickshanks, N., Kleinstreuer, N., van Larebeke, N., Ahmed, N., Ogunkua, O., Krishnakumar, P. K., Vadgama, P., Marignani, P. A., Ghosh, P. M., Ostrosky-Wegman, P., Thompson, P. A., Dent, P., Heneberg, P., Darbre, P., Leung, P. S., Nangia-Makker, P., Cheng, Q., Brooks Robey, R., Al-Temaimi, R., Roy, R., Andrade-Vieira, R., Sinha, R. K., Mehta, R., Vento, R., Di Fiore, R., Ponce-Cusi, R., Dornetshuber-Fleiss, R., Nahta, R., Castellino, R. C., Palorini, R., Hamid, R. A., Langie, S. A. S., Eltom, S. E., Brooks, S. A., Ryeom, S., Wise, S. S., Bay, S. N., Harris, S. A., Papagerakis, S., Romano, S., Pavanello, S., Eriksson, S., Forte, S., Casey, S. C., Luanpitpong, S., Lee, T. J., Otsuki, T., Chen, T., Massfelder, T., Sanderson, T., Guarnieri, T., Hultman, T., Dormoy, V., Odero-Marah, V., Sabbisetti, V., Maguer-Satta, V., Kimryn Rathmell, W., EngstrÃ¶m, W., Decker, W. K., Bisson, W. H., Rojanasakul, Y., Luqmani, Y., Chen, Z., Hu, Z.","Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: The challenge ahead","","36:S254-S296","8eb3e96e-7558-47a2-9664-733377b70d24","","Lifestyle factors are responsible for a considerable portion of cancer incidence worldwide, but credible estimates from the World Health Organization and the International Agency for Research on Cancer (IARC) suggest that the fraction of cancers attributable to toxic environmental exposures is between 7% and 19%. To explore the hypothesis that low-dose exposures to mixtures of chemicals in the environment may be combining to contribute to environmental carcinogenesis, we reviewed 11 hallmark phenotypes of cancer, multiple priority target sites for disruption in each area and prototypical chemical disruptors for all targets, this included dose-response characterizations, evidence of low-dose effects and cross-hallmark effects for all

targets and chemicals. In total, 85 examples of chemicals were reviewed for actions on key pathways/mechanisms related to carcinogenesis. Only 15% (13/85) were found to have evidence of a dose-response threshold, whereas 59% (50/85) exerted low-dose effects. No dose-response information was found for the remaining 26% (22/85). Our analysis suggests that the cumulative effects of individual (non-carcinogenic) chemicals acting on different pathways, and a variety of related systems, organs, tissues and cells could plausibly conspire to produce carcinogenic synergies. Additional basic research on carcinogenesis and research focused on low-dose effects of chemical mixtures needs to be rigorously pursued before the merits of this hypothesis can be further advanced. However, the structure of the World Health Organization International Programme on Chemical Safety 'Mode of Action' framework should be revisited as it has inherent weaknesses that are not fully aligned with our current understanding of cancer biology.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2006","Grant, W. F., Owens, E. T.","Zea mays assays of chemical/radiation genotoxicity for the study of environmental mutagens","","613(1):17-64","354e6238-e327-4c7a-949c-5651e8ba1c33","","From a literature survey, 86 chemicals are tabulated that have been evaluated in 121 assays for their clastogenic effects in Zea mays. Eighty-one of the 86 chemicals are reported as giving a positive reaction (i.e. causing chromosome aberrations). Of these, 36 are reported positive with a dose response. In addition, 32 assays have been recorded for 7 types of radiation, all of which reacted positively. The results of 126 assays with 63 chemicals and 12 types of radiation tested for the inductions of gene mutations are tabulated, as well as 63 chemicals and/or radiation in combined treatments. Three studies reported positive results for mutations on Zea mays seed sent on space flights. The Zea mays (2n = 20) assay is a very good plant bioassay for assessing chromosome damage both in mitosis and meiosis and for somatic mutations induced by chemicals and radiations. The carcinogenicity and Salmonella assays correlate in all cases. The maize bioassay has been shown to be as sensitive and as specific an assay as other plant genotoxicity assays, such as Hordeum vulgare, Vicia faba, Crepis capillaris, Pisum sativum, Lycopersicon esculentum and Allium cepa and should be considered in further studies in assessing clastogenicity. Tests using Zea mays can be made for a spectrum of mutant phenotypes of which many are identifiable in young seedlings. Â© 2006.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2006","Guest, R. K., Ikehata, K., El-Din, M. G., Smith, D. W.","Pesticides and herbicides","","78(10):1755-1801","41cb423a-7b64-45ec-b990-9db40be53344","","","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2015","Guyton, K. Z., Loomis, D., Grosse, Y., El Ghissassi, F., Benbrahim-Tallaa, L., Guha, N., Scoccianti, C., Mattock, H., Straif, K., Blair, A., Fritschi, L., McLaughlin, J., Sergi, C. M., Calaf, G. M., Le Curieux, F., Baldi, I., Forastiere, F., Kromhout, H., t Mannetje, A., Rodriguez, T., Egeghy, P., Jahnke, G. D., Jameson, C. W., Martin, M. T., Ross, M. K., Rusyn, I., Zeise, L.","Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate","","16(5):490-491","225bccba-695d-40b5-95bf-668340d0852b","","","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2006","Hansen, J. M.","Oxidative stress as a mechanism of teratogenesis","","78(4):293-307","fdf600e9-d2d9-4bbd-b0f0-a1eb2c7a3eaa","","Emerging evidence shows that redox-sensitive signal transduction pathways are critical for developmental processes, including proliferation,

differentiation, and apoptosis. As a consequence, teratogens that induce oxidative stress (OS) may induce teratogenesis via the misregulation of these same pathways. Many of these pathways are regulated by cellular thiol redox couples, namely glutathione/glutathione disulfide, thioredoxin red/thioredoinox, and cysteine/cystine. This review outlines oxidative stress as a mechanism of teratogenesis through the disruption of thiol-mediated redox signaling. Due to the ability of many known and suspected teratogens to induce oxidative stress and the many signaling pathways that have redox-sensitive components, further research is warranted to fully understand these mechanisms. Â© 2007 Wiley-Liss, Inc.","","","RefMan","","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2011","Hariri, A. T., Moallem, S. A., Mahmoudi, M., Hosseinzadeh, H.","The effect of crocin and safranal, constituents of saffron, against subacute effect of diazinon on hematological and genotoxicity indices in rats","","18(6):499-504","684865a8-78f2-4c66-9e12-9e16008b1661","","In this study, the effect of crocin and safranal was studied against subacute toxicity of diazinon (DZN) on hematological and genotoxicity indices in rats. The rats were divided into 16 groups consisted of 6 rats in control, diazinon, vitamin E, vitamin E and DZN, crocin (3 doses), crocin (3 doses) and DZN, safranal (3 doses), safranal (3 doses) and DZN groups. Vitamin E (200 IU/kg), safranal at doses 0.025, 0.05 and 0.1 ml/kg and crocin at doses 50, 100 and 200 mg/kg were injected intraperitoneally to rats three times per week alone or with DZN (20 mg/kg/day, orally) for 4 weeks. Hematological parameters were evaluated at the end of 4 weeks. The evaluation of genotoxicity was done using the micronucleus assay. Vitamin E and, at lower doses, safranal (0.025 and 0.05 ml/kg) and crocin (50 mg/kg) restored the reduction of red blood cell, hemoglobin and hematocrit indices induced by DZN. These agents at some doses also prevented the reduction in platelets counts indices in diazinon treated group. A significant increase in reticulocyte was induced by diazinon. Vitamin E, safranal (0.025 or 0.05 ml/kg) and all doses of crocin decreased this effect of diazinon. In all doses vitamin E, crocin and safranal did not inhibit the effect of diazinon on RBC cholinesterase activity. A significant increase in micronucleus indices was seen with diazinon. Vitamin E, safranal and crocin could not prevent this genotoxicity. This study showed that vitamin E, safranal and crocin (without effects on cholinesterase) reduced diazinon hematological toxicity, but they did not prevent the genotoxicity induced by diazinon. Â© 2010 Elsevier GmbH. All rights reserved.","","","RefMan","","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2006","Hartley, C. J., Newcomb, R. D., Russell, R. J., Yong, C. G., Stevens, J. R., Yeates, D. K., La Salle, J., Oakeshott, J. G.","Amplification of DNA from preserved specimens shows blowflies were preadapted for the rapid evolution of insecticide resistance","","103(23):8757-8762","59b1c922-3253-4f41-9a5c-a261946c2fe2","","Mutations of esterase 3 confer two forms of organophosphate resistance on contemporary Australasian Lucilia cuprina. One form, called diazinon resistance, is slightly more effective against commonly used insecticides and is now more prevalent than the other form, called malathion resistance. We report here that the single amino acid replacement associated with diazinon resistance and two replacements associated with malathion resistance also occur in esterase 3 in the sibling species Lucilia sericata, suggesting convergent evolution around a finite set of resistance options. We also find parallels between the species in the geographic distributions of the polymorphisms: In both cases, the diazinon-resistance change is absent or rare outside Australasia where insecticide pressure is lower, whereas the changes associated with malathion resistance are widespread. Furthermore, PCR analysis

of pinned specimens of Australasian L. cuprina collected before the release of organophosphate insecticides reveals no cases of the diazinon-resistance change but several cases of those associated with malathion resistance. Thus, the early outbreak of resistance in this species can be explained by the preexistence of mutant alleles encoding malathion resistance. The pinned specimen analysis also shows much higher genetic diversity at the locus before organophosphate use, suggesting that the subsequent sweep of diazinon resistance in Australasia has compromised the scope for the locus to respond further to the ongoing challenge of the insecticides. Â© 2006 by The National Academy of Sciences of the USA.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2000","Hatjian, B. A., Mutch, E., Williams, F. M., Blain, P. G., Edwards, J. W.","Cytogenetic response without changes in peripheral cholinesterase enzymes following exposure to a sheep dip containing diazinon in vivo and in vitro","Mutation research","472(1-2):85-92","36b78a60-985d-4e88-b6ec-f71aa7867422","","Occupational exposure to organophosphorus insecticides (OPs), such as diazinon, may be monitored by the measurement of the activity of peripheral cholinesterase enzymes, including erythrocyte acetylcholinesterase (EAChE) and plasma or serum cholinesterase (plasma or serum ChE). Exposures have also been measured by the analysis of dialkyl phosphate metabolites of OPs in urine. The potential health risks associated with exposure, especially those of a neurological nature, may then be estimated, and appropriate measures to reduce or eliminate exposures can be implemented. There is evidence that some OP pesticides may have in vivo genotoxic effects, suggesting a possible link with cancer with long term or repeated heavy exposures. This paper describes work performed in 17 subjects with a single or two exposures to a sheep dip containing diazinon. Urine samples revealed OP metabolites dimethylphosphate (DMP), dimethylthiophosphate (DMTP), diethylphosphate (DEP) and diethylthiophosphate (DETP) in 37% of subjects at low levels which were not elevated after exposure. EAChE and plasma ChE were also unchanged before and after exposure, and were similar to those measured in unexposed control groups. Sister chromatid exchanges (SCE), a marker of chromosome damage, was significantly elevated in peripheral blood lymphocytes after exposure compared with before. SCE were unchanged in a group of non-occupationally exposed workers. In vitro studies with both authentic diazinon (98%) and diazinon in a sheep dip formulation (45%) showed increased SCE and decreased replicative indices, suggesting toxic and genotoxic effects of diazinon.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2015","How, V., Hashim, Z., Ismail, P., Omar, D., Md Said, S., Tamrin, S. B. M.","Characterization of risk factors for DNA damage among paddy farm worker exposed to mixtures of organophosphates","","70(2):102-109","7ec3b031-3980-4a9e-acc7-574fbb1e0484","","This is a cross-sectional study conducted among paddy farmers to characterize potential risk factors that influence levels of DNA damage from exposure to mixtures of organophosphates. Comet assay was used to determine the level of DNA damage by measuring the comet tail length from the exfoliated buccal mucosa. The result suggests that farmers who chronically exposure to a mixture of organophosphates has at least 2-fold significant increase of DNA damage as compared with control group. Factor analysis and linear regression both suggest that DNA damage reported by farmers may influence individual, occupational, and residential factors and are reported as significant predictor factors, whereas this effect is mainly caused by individual factors among the control group. The findings of the present study suggest that either farmer or control group bear certain extent of

genotoxic burden contributed by different risk
factors.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2003","Jarvik, G. P., Jampsa, R., Richter, R. J., Carlson, C. S., Rieder, M. J., Nickerson, D. A., Furlong, C. E.","Novel paraoxonase (PON1) nonsense and missense mutations predicted by functional genomic assay of PON1 status","Pharmacogenetics","13(5):291-5","c4792725-f124-4280-8751-b6ddc8dd8d37","","Paraoxonase (PON1) has been termed an environmental response enzyme for its function in the detoxification of organophosphate pesticides, nerve agents and pharmaceuticals such as glucocorticoids and statins, as well as its cardioprotective role in breaking down oxidized LDL. PON1(192) genotype can be predicted with high accuracy from an examination of the two-dimensional plot of paraoxon and diazoxon hydrolysis rates [1]. Individuals for whom this functional genomic assay failed to predict PON1(192) genotype, or who had a low PON activity relative to others with the same genotype, were predicted to have genetic alterations that explained the inconsistency. Sequencing of the PON1 region of 23 Caucasian individuals detected a nonsense mutation changing amino acid 194 from a Trp to a stop codon (PON1(Trp194stop)). It was predicted that subjects who genotyped as PON1(192QR) but phenotyped as PON1(192QQ) or PON1(192RR) might carry the protein truncation mutation for which the defective product failed to be detected by the phenotyping assay. Screening of the five discordant subjects resulted in the detection of a single Caucasian carrying the stop codon, and determined its phasing on the PON1(192R) allele. Sequencing confirmed the change and revealed an additional subject with a likely deletion of the 5' end of the PON1 gene. Additional sequencing of 25 subjects with low PON1 activities identified two additional previously undescribed PON1 mutations, which may affect PON1 function: PON1(Pro90Leu) associated with the PON1(192Q) allele and PON1(Asp124missplice) associated with the PON1(192R)
allele.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","1999","Josse, D., Xie, W., Masson, P., Lockridge, O.","Human serum paraoxonase (PON1): identification of essential amino acid residues by group-selective labelling and site-directed mutagenesis","Chemico-biological interactions","119-120:71-8","0db7ed66-fed2-449d-a66e-7701e2a398dc","","Human serum paraoxonase/arylesterase (PON1, EC 3.1.8.1.) is a calcium-dependent enzyme which hydrolyzes a wide variety of organophosphates, including paraoxon, DFP, sarin and soman. Although the 3-D structure of PON has not yet been determined and its sequence shows no similarity with any other crystallized proteins, we undertook to identify some of its essential amino acid residues by two complementary approaches: group-specific labelling and site-directed mutagenesis. Group-specific labelling studies, performed on the purified native enzyme, indicated that one or more Trp, His and Asp/Glu are potentially important residues for PON activity. Based on these results, we identified some of these residues, conserved in the sequenced mammalian PON1, by site-directed mutagenesis. PON1 mutants were transiently expressed in 293T cells. The catalytic constants k(cat) and Km (relative to k(cat) and Km of the wild-type) determined with four different substrates (phenylacetate, paraoxon, diazoxon, chlorpyrifos oxon), were not significantly changed for the following mutants: W193A, W201A, W253A, H160N, H245N, H250N, H347N, E32A, E48A, D88A, D107A, D121A, D273A. By contrast, k(cat) was less than 1% for eight mutants: W280A, H114N, H133N, H154N, H242N, H284N, E52A and D53A. The essential amino acid residues identified in this work could be part of the PON1 active site, acting either as calcium ligands (E52 and D53?)

or as substrate binding (W280?) or nucleophilic (His residues?) sites. However, we cannot rule out that the effects of mutations on catalytic properties resulted from a remote conformational change and/or misfolding of mutant proteins.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2016","Karamian, A., Shokrzadeh, M., Ahmadi, A.","The potential chemoprotective effects of melatonin against genotoxicity induced by diazinon in human peripheral blood lymphocytes","","32(2):360-366","2da524cd-89fb-4b55-9c03-6d94fd75a59c","","The protection afforded by melatonin (MLT) against diazinon (DZN)-induced micronucleus formation, an index of DNA damage, in human blood lymphocytes was investigated. Whole blood samples were collected from five volunteers and were incubated with MLT at different concentrations (100, 200, 300, and 400 Î¼M final concentration) for 1 h. The samples were then incubated with 750 Î¼M DZN for 1 h. Subsequently, the lymphocytes were cultured with a mitogenic stimulant to evaluate micronucleus formation in cytokinesis-blocked binucleated cells. The incubation of lymphocytes with DZN induces additional genotoxicity. Pretreatment with MLT at these doses significantly reduced the micronucleus frequency in cultured lymphocytes ($p < 0.05$-$p < 0.0001$). The maximum decrease in the frequency of micronuclei was observed at 400 Î¼M of MLT, which caused a reduction of 87%. MLT also exhibited an excellent and dose-dependent radical-scavenging activity against 1,1-diphenyl-2-picrylhydrazyl free radicals. Our study revealed that MLT has a potent antigenotoxic effect against DZN-induced DNA damage, which may be due to the scavenging of free radicals and increased antioxidant status. Because MLT is a natural compound and is considered safe, it can be used as a supplement to protect people exposed to chemical or environmental hazards.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2008","Kashanian, S., Gholivand, M. B., Ahmadi, F., Ravan, H.","Interaction of Diazinon with DNA and the protective role of selenium in DNA damage","","27(6):325-332","0ba07166-a8d4-4059-be6e-487018068cc0","","The interaction of native calf thymus DNA with Diazinon, an organophophorus insecticide, in HEPES buffer at neutral pH, was monitored by UV absorption spectrophotometry, circular dichroism (CD), electrochemical technique, and fluorescence spectroscopy. UV spectra showed hyperchromicity and blue shift with the increase of Diazinon concentration. Fluorescence spectroscopy results indicated that the probable quenching mechanism of DNA-ethidium bromide (EB) fluorescence by Diazinon is a dynamic quenching procedure, because the Stern-Volmer quenching constant (KSV) increased with the temperature rising. Unchanging of the CD signal around 280 nm with increasing ratio of Diazinon to DNA is an important evidence for non-intercalative-binding mode of Diazinon with DNA. Stoichiometry measurement of the DNA-nDiazinon indicated that a stable 1:2 complex of DNA-Diazinon was formed under the selected conditions. The electrochemical study of the Diazinon-DNA interaction was carried out by incubation of DNA with Diazinon in the presence of varying amounts of selenium (Se). This technique revealed that Se is able to diminish the DNA damage effect of Diazinon. Â© Copyright 2008, Mary Ann Liebert, Inc.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Kashanian, S., Gholivand, M. B., Ahmadi, F., Ravan, H.","Erratum: Interaction of diazinon with DNA and the protective role of selenium in DNA damage (DNA and Cell Biology (2008) 27:6 (325-332))","","31(3):414","2d86e429-81e6-4e68-8c56-a239d9b67900","","","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2005","Kirpnick, Z., Homiski, M.,

Rubitski, E., Repnevskaya, M., Howlett, N., Aubrecht, J., Schiestl, R. H.","Yeast DEL assay detects clastogens","Mutation research","582(1-2):116-34","77b626ee-dd52-4e55-8967-be439c705335","","Chromosomal rearrangements, including DNA deletions are involved in carcinogenesis. The deletion (DEL) assay scoring for DNA deletions in the yeast Saccharomyces cerevisiae is able to detect a wide range of carcinogens. Among approximately 60 compounds of known carcinogenic activity, the DEL assay detected 86% correctly whereas the Ames Salmonella assay detected only 30% correctly [R.J. Brennan, R.H. Schiestl, Detecting carcinogens with the yeast DEL assay, Methods Mol. Biol. 262 (2004) 111-124]. Since the DEL assay is highly inducible by DNA double strand breaks, this study examined the utility of the DEL assay for detecting clastogens. Ten model compounds, with varied mechanisms of genotoxicity, were examined for their effect on the frequency of DNA deletions with the DEL assay. The compounds tested were: actinomycin D, camptothecin, methotrexate and 5-fluorodeoxyuridine, which are anticancer agents, noscapine and furosemide are therapeutics, acridine, methyl acrylate and resorcinol are industrial chemicals and diazinon is an insecticide. The in vitro micronucleus assay (IVMN) in CHO cells, a commonly used tool for detection of clastogens, was performed on the same compounds and the results of the two assays were compared. The results of our study show that there is 70% concordance in the presence of metabolic activation (rat liver S9) and 80% concordance in the absence of metabolic activation between the DEL assay and the standard in vitro micronucleus assay. The lack of cytotoxicity observed for four of the ten compounds examined indicates limited diffusion of lipophilic compounds across the yeast cell wall. Thus, the development of a more permeable yeast tester strain is expected to greatly improve concordance of the DEL assay with the IVMN assay. The yeast DEL assay is inexpensive, amenable to automation and requires less expertise to perform than the IVMN. Thus, it has a strong potential as a robust, fast and economical screen for detecting clastogens in vitro.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Lee, W. J., Kim, S. C., Lee, S. J., Lee, J., Park, J. H., Yu, K. S., Lim, J., Kwon, S. W.","Investigating the different mechanisms of genotoxic and non-genotoxic carcinogens by a gene set analysis","","9(1)","0a6d8604-950d-4302-9e24-e290b4ac7a5d","","Based on the process of carcinogenesis, carcinogens are classified as either genotoxic or non-genotoxic. In contrast to non-genotoxic carcinogens, many genotoxic carcinogens have been reported to cause tumor in carcinogenic bioassays in animals. Thus evaluating the genotoxicity potential of chemicals is important to discriminate genotoxic from non-genotoxic carcinogens for health care and pharmaceutical industry safety. Additionally, investigating the difference between the mechanisms of genotoxic and non-genotoxic carcinogens could provide the foundation for a mechanism-based classification for unknown compounds. In this study, we investigated the gene expression of HepG2 cells treated with genotoxic or non-genotoxic carcinogens and compared their mechanisms of action. To enhance our understanding of the differences in the mechanisms of genotoxic and non-genotoxic carcinogens, we implemented a gene set analysis using 12 compounds for the training set (12, 24, 48 h) and validated significant gene sets using 22 compounds for the test set (24, 48 h). For a direct biological translation, we conducted a gene set analysis using Globaltest and selected significant gene sets. To validate the results, training and test compounds were predicted by the significant gene sets using a prediction analysis for microarrays (PAM). Finally, we obtained 6 gene sets, including sets enriched for genes involved in the adherens junction, bladder

cancer, p53 signaling pathway, pathways in cancer, peroxisome and RNA degradation. Among the 6 gene sets, the bladder cancer and p53 signaling pathway sets were significant at 12, 24 and 48 h. We also found that the DDB2, RRM2B and GADD45A, genes related to the repair and damage prevention of DNA, were consistently up-regulated for genotoxic carcinogens. Our results suggest that a gene set analysis could provide a robust tool in the investigation of the different mechanisms of genotoxic and non-genotoxic carcinogens and construct a more detailed understanding of the perturbation of significant pathways. Â© 2014 Lee et al.","","","RefMan","","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2003","Li, A. Y., Guerrero, F. D., Almazan Garcia, C., George, J. E.","Survey of resistance to permethrin and diazinon and the use of a multiplex polymerase chain reaction assay to detect resistance alleles in the horn fly, Haematobia irritans irritans (L.)","Journal of medical entomology","40(6):942-9","ed064795-f73f-4469-b94f-c513a3287e97","","A field survey was conducted in 2001 to evaluate resistance to pyrethroid and organophosphate (OP) insecticides on horn flies, Hematobia irritans irritans (L.), from seven ranches in the state of Tamaulipas, Mexico, and from three locations in central Texas. Filter papers impregnated with either technical permethrin or diazinon were used to measure the levels of resistance to pyrethroids and OPs. A multiplex polymerase chain reaction (PCR) assay was used on individual horn flies from these field populations to detect the presence of the kdr and super-kdr alleles associated with pyrethroid resistance, and a mutated alphaE7 esterase allele associated with OP resistance. Relative to a susceptible laboratory (Kerrville) strain, horn flies from Mexico exhibited 5.1- to 28.3-fold resistance to permethrin at the LC50, and 23.8- to 136-fold resistance at the LC90. Horn flies from Texas ranches exhibited only two- to five-fold resistance. All field populations of the horn fly were highly susceptible to diazinon, and no mutant alphaE7 esterase alleles were detected. The super-kdr allele was found only in a single fly from a ranch in Mexico. Results of PCR assays showed that the kdr allele was present at various frequencies in field populations of horn flies. A gender-related bias in distribution of kdr genotypes was found in horn flies from Mexico, but not in horn flies from Texas. The overall kdr allelic frequencies in horn flies from Mexico were 23.2-37.8% higher in females than in males. Regression analysis revealed a significant correlation between kdr allelic frequencies and the levels of knockdown resistance to permethrin among the horn fly populations studied. The results validate the role of the PCR-based molecular assay as a diagnostic tool in monitoring resistance to pyrethroids and also provide useful information on population genetics of horn fly resistance to pyrethroids and OPs.","","","RefMan","","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2014","Malathi, M., Ramya Devi, D., Vedha Hari, B. N.","Crocus sativus Linn - A potential source for diverse therapeutic applications","","26(2):299-305","b5f8ad42-caa2-4c13-a457-375d2b252494","","The dried red stigma of Crocus sativus L. belonging to Iridaceae family is a variety of spice commercially named as Saffron. It consists of more than 150 volatile compounds chiefly the terpenes and their esters and it belongs to native of Greece and South west Asia. Saffron has the medicinally important activities such as anticancer, anti-inflammatory, antitussive, antioxidant, anxiolytic, aphrodisiac, antinociceptive, anticonvulsant, antihypertensive, antidepressant, antigenototoxic and relaxant activity. Literatures suggest extraction method like hydro distillation using cold, hot water and ethanol for collecting the active components of the leaves and flowers of Crocus sativus L. (saffron). The collected essential oil and other chemical constituents were

investigated by the researchers by using GC/MS technique. The objective of this review is to highlight the salient features, biological activities and extraction methods for the active components of the plant.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2006","Mankame, T., Hokanson, R., Fudge, R., Chowdhary, R., Busbee, D.","Alteration of gene expression in human cells treated with the agricultural chemical diazinon: Possible interaction in fetal development","","25(5):225-233","9d2c8e9b-93bf-42d6-818d-140092a8580f","","Agricultural chemicals frequently alter human health or development, typically because they have endocrine agonist or antagonist activities and alter hormone-regulation of gene expression. The insecticide, diazinon, was evaluated for gene expression disrupting activity using MCF-7 cells, an estrogen-dependent human cell line, to examine the capacity of the insecticide to disrupt gene expression essential for morphological development, immune system development or function, and/or central nervous system development and function. MCF-7 cells were treated with 30, 50 or 67 ppm diazinon, and gene expression was measured in treated cells compared to expression in untreated or estrogen-treated cells. DNA microarray analysis of diazinon-treated cells showed significant up- or down-regulation of a large number of genes compared to untreated cells. Of the 600 human genes on the Phase 1 chip utilized for these studies, two specific genes - calreticulin and TGF-Î²3 - were selected for corroboration using quantitative real time PCR (qrtPCR). qrtPCR, completed to assess gene expression levels for calreticulin and TGFÎ²3, confirmed results showing significant up-regulation of these two genes obtained from the microarray data. These studies were designed to provide baseline data on the gene expression-altering capacity of a specific chemical, diazinon, and allow a partial assessment of the potentially deleterious effects associated with exposure of human cells to this chemical. Currently, it is not known whether results from cells in vitro can be extrapolated to human health consequences of chemical exposure. Â© 2006 Edward Arnold (Publishers) Ltd.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2011","Matthews, A. R., Sutter, M. E., Rentz, D. E.","Serum Paraoxonase-1 (PON-1) Genotype and Exposure to Organophosphorous Insectides-Is There a High-Risk Population?","","7(3):243-247","428d4bd7-1c5b-432b-95d3-50b0f088d9fc","","The Health Studies Branch (HSB) is responsible for responding to domestic and international requests for assistance with suspected and known environmental-associated public health threats as well as pursuing original environmental research. The HSB employs personnel with a wide variety of educational backgrounds and professional training including epidemiology, medicine, toxicology, statistics, and other environmental public health-related disciplines. This wide range of expertise is necessary to address the broad scope of potential environmental health threats. HSB scientists conduct studies on environmental exposures. Recent examples include the following: mercury exposure in children living in large urban areas, exposure to brevetoxins and microcystins arising from harmful algal blooms, and occupational exposures to pesticides. This article will present a brief description of an ongoing study of insecticide exposure and paraoxonase-1 (PON-1) genotype in banana plantation workers in Chinandega, Nicaragua. We will then discuss the enzyme PON-1 and its potential role in organophosphate insecticide metabolism and toxicity. Â© 2011 American College of Medical Toxicology.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2008","Mehrani, H., Golmanesh, L.","Changes in mRNA and protein levels of nicotinic acetylcholine receptors in

Diazoxon exposed pC12 cells","Toxicology in vitro : an international journal published in association with BIBRA","22(5):1257-63","cd0a2294-5db1-4a72-b2f3-b0fab781d180","","Effects of diazoxon on the gene and protein expression of nicotinic acetylcholine receptors (nAChR) were evaluated in PC12 cells. Cells were exposed to 100 microM diazoxon for 48 h in the presence versus absence of nAChR agonists or antagonists. Diazoxon significantly inhibited AChE activity in the cells. At the mRNA level, transcripts of the alpha4 and beta2 subunits of nAChR were significantly reduced in cells exposed to diazoxon, but there was no change in alpha7 subunit mRNA content. Diazoxon exposure also significantly reduced the protein levels of both alpha4 and beta2 nAChR subunits. Treatment with nicotine (10 microM) or with the nicotinic receptor antagonists, mecamylamine (10 microM) or dihydro-beta-erythroidine (DHbetaE) (5 microM) efficiently prevented the diazoxon-induced reduction in alpha4 and beta2 nAChR mRNA and protein in PC12 cells, but carbamaylcholine, a weak nAChR agonist, was ineffective. These data suggest that alpha4beta2 nAChRs are involved in diazoxon-related toxicity and that nicotinic receptor antagonists could play a protective role against organophosphate-related damage.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Mironidis, G. K., Kapantaidaki, D., Bentila, M., Morou, E., Savopoulou-Soultani, M., Vontas, J.","Resurgence of the cotton bollworm Helicoverpa armigera in northern Greece associated with insecticide resistance","","20(4):505-512","140d4f39-40e2-4d5c-8f68-4645ba2f3f29","","Helicoverpa armigera has been controlled effectively with chemical insecticides in the major cotton crop production areas of northern Greece for many years. However, a resurgence of the pest was observed in 2010, which significantly affected crop production. During a 4-year survey (2007-2010), we examined the insecticide resistance status of H. armigera populations from two major and representative cotton production areas in northern Greece against seven insecticides (chlorpyrifos, diazinon, methomyl, alpha-cypermethrin, cypermethrin, gamma-cyhalothrin and endosulfan). Full dose-response bioassays on third instar larvae were performed by topical application. Lethal doses at 50% were estimated by probit analysis and resistance factors (RF) were calculated, compared to a susceptible laboratory reference strain. Resistance levels were relatively moderate until 2009, with resistance ratios below 10-fold for organophosphates and carbamates and up to 16-fold for the pyrethroid alpha-cypermethrin. However, resistance rose to 46- and 81-fold for chlorpyrifos and alpha-cypermethrin, respectively in 2010, when the resurgence of the pest was observed. None of the known pyrethroid resistance mutations were found in the pyrethroid-resistant insects. The possible association between resistance and H. armigera resurgence in Greece is discussed. Â© 2012 Institute of Zoology, Chinese Academy of Sciences.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Mosqueira, B., Soma, D. D., Namountougou, M., Poda, S., Diabate, A., Ali, O., Fournet, F., Baldet, T., Carnevale, P., Dabire, R. K., Mas-Coma, S.","Pilot study on the combination of an organophosphate-based insecticide paint and pyrethroid-treated long lasting nets against pyrethroid resistant malaria vectors in Burkina Faso","Acta tropica","148:162-9","8bc7fc8f-5eab-4165-943c-448510c7119f","","A pilot study to test the efficacy of combining an organophosphate-based insecticide paint and pyrethroid-treated Long Lasting Insecticide Treated Nets (LLINs) against pyrethroid-resistant malaria vector mosquitoes was performed in a real village setting in Burkina Faso. Paint Inesfly 5A IGR, comprised of two organophosphates (OPs) and an Insect Growth Regulator (IGR), was tested in

combination with pyrethroid-treated LLINs. Efficacy was assessed in terms of mortality for 12 months using Early Morning Collections of malaria vectors and 30-minute WHO bioassays. Resistance to pyrethroids and OPs was assessed by detecting the frequency of L1014F and L1014S kdr mutations and Ace-1(R)G119S mutation, respectively. Blood meal origin was identified using a direct enzyme-linked immunosorbent assay (ELISA). The combination of Inesfly 5A IGR and LLINs was effective in killing 99.9-100% of malaria vector populations for 6 months regardless of the dose and volume treated. After 12 months, mortality rates decreased to 69.5-82.2%. The highest mortality rates observed in houses treated with 2 layers of insecticide paint and a larger volume. WHO bioassays supported these results: mortalities were 98.8-100% for 6 months and decreased after 12 months to 81.7-97.0%. Mortality rates in control houses with LLINs were low. Collected malaria vectors consisted exclusively of Anopheles coluzzii and were resistant to pyrethroids, with a L1014 kdr mutation frequency ranging from 60 to 98% through the study. About 58% of An. coluzzii collected inside houses had bloodfed on non-human animals. Combining Inesfly 5A IGR and LLINs yielded a one year killing efficacy against An. coluzzii highly resistant to pyrethroids but susceptible to OPs that exhibited an anthropo-zoophilic behaviour in the study area. The results obtained in a real setting supported previous work performed in experimental huts and underscore the need to study the impact that this novel strategy may have on clinical malaria and malaria exposure in children in a similar area of high pyrethroid resistance in South-Western Burkina Faso.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Mostafalou, S., Abdollahi, M.","Pesticides and human chronic diseases: Evidences, mechanisms, and perspectives","","268(2):157-177","8ffd29d3-5b82-4e68-bd96-ed463caede6c","","Along with the wide use of pesticides in the world, the concerns over their health impacts are rapidly growing. There is a huge body of evidence on the relation between exposure to pesticides and elevated rate of chronic diseases such as different types of cancers, diabetes, neurodegenerative disorders like Parkinson, Alzheimer, and amyotrophic lateral sclerosis (ALS), birth defects, and reproductive disorders. There is also circumstantial evidence on the association of exposure to pesticides with some other chronic diseases like respiratory problems, particularly asthma and chronic obstructive pulmonary disease (COPD), cardiovascular disease such as atherosclerosis and coronary artery disease, chronic nephropathies, autoimmune diseases like systemic lupus erythematous and rheumatoid arthritis, chronic fatigue syndrome, and aging. The common feature of chronic disorders is a disturbance in cellular homeostasis, which can be induced via pesticides' primary action like perturbation of ion channels, enzymes, receptors, etc., or can as well be mediated via pathways other than the main mechanism. In this review, we present the highlighted evidence on the association of pesticide's exposure with the incidence of chronic diseases and introduce genetic damages, epigenetic modifications, endocrine disruption, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress and unfolded protein response (UPR), impairment of ubiquitin proteasome system, and defective autophagy as the effective mechanisms of action. Â© 2013 Elsevier Inc.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Mostafalou, S., Karami-Mohajeri, S., Abdollahi, M.","Environmental and population studies concerning exposure to pesticides in Iran: A comprehensive review","","15(12)","ff42eec2-c04f-47f0-8340-a4a57165e084","","Pesticides are widely used in Iranian agriculture and this has made a major toxicological concern among health professionals. The objective of this study is

to explore national data about pesticides toxicity. All relevant databases such as Google Scholar, PubMed, and Scopus in a time period of 1960 to 2012 were searched for the keywords ""Pesticides, Iran, Environment, and Population studies"". A total of 57 studies were found relevant and then included into study. Almost all non-experimental studies carried out in Iran were classified into two main categories of residue assessment in different samples and toxic effects on human. Depending on the dose and duration of exposure, toxic effects of pesticides have been studied in two classifications including acute toxicity or acute poisoning and chronic toxicity. High extent of pesticides have been used during the past decade in Iran while no enough proper studies were done to explore their possible toxic effects in the environment and the people.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2015","Muranli, F. D., Kanev, M., Ozdemir, K.","Genotoxic effects of diazinon on human peripheral blood lymphocytes","Arhiv za higijenu rada i toksikologiju","66(2):153-8","d11c191f-53a7-4523-a01c-880daa4c7e48","","The aim of this study was to evaluate the genetic damage in human peripheral blood lymphocytes following 24 and 48- hour exposure to a commercial diazinon formulation Basudin 60EM(R) at concentrations between 0.01 and 40 mug mL-1. For this purpose we used the micronucleus (MN), fluorescence in situ hybridization (FISH), and alkaline single cell gel electrophoresis (comet) assay. Diazinon significantly increased the frequency of micronucleated cells compared to control. Forty-eight-hour exposure increased this frequency even at lower concentrations (0.01-10 mug mL-1). The FISH results revealed aneugenic effects at 10 mug mL-1. The comet assay also confirmed DNA damage at concentrations between 10 and 40 mug mL-1. Our findings have confirmed the genotoxic potential of diazinon and its cytotoxic effect on human lymphocytes. The increased DNA damage in our study raises concern about the current assessment of the health risk posed by this pesticide and calls for a high level of caution in agricultural and household use.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2011","Muranli, F. D. G.","Human lymphocyte micronucleus genotoxicity test with an organophosphorus pesticide diazinon","","19:S121-S122","d66d43a1-9d34-4faa-b3db-20b5929637b5","","In the present study, the genotoxic effects of commercial formulation of an organophosphorus pesticide Diazinon (Basudin 60EM) were investigated using cytokinesis block micronucleus assay in cultured human peripheral blood lymphocytes. Cells were treated with 0.01, 0.1, 1, 5, and 10 Î¼g/ml concentrations of Diazinon for 24 and 48 h. As a result of the study, Diazinon significantly increased micronucleus frequency and decreased cytokinesis block proliferation index. The results indicate that Diazinon has a genotoxic potential in cultured human peripheral blood lymphocytes.","","","RefMan","","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2012","Muranli, F. D. G.","Assessment of aneugenic potential of diazinon in human peripheral blood lymphocytes by using fluorescence in situ hybridization","","63:55","6056d107-a610-4008-93ad-f4bceb6fad13","","In the present study, clastogenic and aneugenic effects of commercial formulation of an organophosphorous pesticide diazinon (Basudin 60EM) were investigated using cytokinesis-block micronucleus (CBMN) and fluorescence in situ hybridisation (FISH) method in cultured human peripheral blood lymphocytes. In order to discriminate MN produced by agents causing chromosome breakage (clastogens) from those arising following treatment with agents causing spindle malfunctioning (aneugen), FISH with centromere-specific Î±-satellite DNA probe was used. Cells were treated with 5 Î¼g mL-1

and 10 Î¼g mL-1 of diazinon for 48 hours. Vinblastine sulphate (0.1 Î¼g mL-1) was used as positive control. The slides that were prepared using CBMN assay were used in FISH assay. FISH was performed using an Î±-satellite probe for all human centromeres (PanCentromeric primeFISHÂ® - DIAGEN). After slides were pretreated with RNase, HCL, and pepsin, denaturation of slide and probe was done by baking on a 70 Â°C hot block. They were hybridised for one night at 37 Â°C and counterstained with DAPI. The slides were observed with fluorescence microscope using 360 nm, 460 nm, and 510 nm excitation filters. The classification of MN was restricted to cells whose nuclei showed bright fluorescent spots. The presence of centromere-positive MN (C+MN) in treated cultures was compared with controls with a one-tailed Fisher's exact test. The percentage of C+MN values were (69.3Â±0.6) %, (82.0Â±2.8) %, (68.7Â±1.6) %, (81.0Â±5.5) % for negative control, positive control, 5 Î¼g mL-1, and 10 Î¼g mL-1 diazinon, respectively. As a result of the study, diazinon has aneugenic effect at 10 Î¼g mL-1 in cultured human peripheral blood lymphocytes.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Najafi, G., Karimi, A., Zobeiri, F., Babaei, M., Najafi, A.","Protective Effect of Selenium on Diazinon Induced sperm DNA damage and decrease of sperm count, sperm viability and velocity","","10:91","2c265009-abc1-4557-aef8-b830dda4239f","","Diazinon (DZN) is an insecticide witch is widely used in agriculture and to control pests in the environment; this compound can be highly toxic for animals and human kind. DZN is characterized in organophosphate (OP) agrochemicals. To evaluate the effect of selenium (SE) as a potential antioxidant on diazinon (DZN) induced histopathological damages, 54 mature male rats were used. The animals were assigned into 3 groups including control-sham, DZN alone and SE+DZN groups. The control-sham group received corn oil and the animals in DZN and SE+DZN groups received 300 mg/kg and 6 microgram/rat, orally, once a day for 60 days respectively. Immature, immotile, death and DNA damaged sperms number increased in DZN exposure animals. Total sperm count decreased by the time in all DZN-exposed animals. The animals, which exposed to SE+DZN, Immature, immotile, death and DNA damaged sperms number was significantly lower in number in comparison to DZN cases. Observations demonstrated that the percentage of morphologically abnormal sperms significantly (p<0.05) increased by the time in DZN exposed animals.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2005","Newcomb, R. D., Gleeson, D. M., Yong, C. G., Russell, R. J., Oakeshott, J. G.","Multiple mutations and gene duplications conferring organophosphorus insecticide resistance have been selected at the Rop-1 locus of the sheep blowfly, Lucilia cuprina","Journal of molecular evolution","60(2):207-20","6d05b8a9-ffe5-4d6c-816e-a6747f5a1abf","","Sequences of the esterase gene alpha E7 were compared across 41 isogenic (IV) strains of the sheep blowfly, Lucilia cuprina, and one strain of the sibling species, L. sericata. The 1.2-kb region sequenced includes sites of two insecticide resistance mutations. Gly137Asp confers resistance to organophosphorus insecticides (OPs), particularly preferring diethyl OPs such as diazinon, while Trp251Leu prefers dimethyl OPs, and particularly malathion, with the additional presence of carboxylester moieties. We found that there are just eight haplotypes among the 41 chromosomes studied: two Gly137Asp containing haplotypes, two Trp251Leu containing haplotypes, and four susceptible haplotypes, including the L. sericata sequence. While phylogenetic analysis of these haplotypes suggests that the Asp137 and Leu251 mutations each arose at least twice, evidence for recombination was detected across the region, therefore single origins for these

resistance mutations cannot be ruled out. Levels of linkage disequilibrium in the data are high and significant hitchhiking is indicated by Fay and Wu' s H test but not the Tajima test. A test of haplotype diversity indicates a paucity of diversity compared with neutral expectations. Both these results are consistent with a very recent selective sweep at the Lc alphaE7 locus. Interestingly, gene duplications of three different combinations of OP resistant haplotypes were identified in seven of the isogenic (IV) strains. All three types of duplication involve an Asp137 and a Trp251 haplotype. To examine whether more haplotypes existed before the hypothesised selective sweep, fragments of alpha E7 surrounding the resistance mutations were amplified from pinned material dating back to before OPs were used. Four new sequence haplotypes, not sampled in the survey of extant haplotypes, were obtained that are all associated with susceptibility. This is suggestive of a higher historical level of susceptible allelic diversity at this locus.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2014","O'Flaherty, C.","Iatrogenic genetic damage of spermatozoa","Adv. Exp. Med. Biol.","791:117-135","fb387ae1-61ba-4b9a-ba1f-ee43d8f9b83a","","Various factors that negatively influence male fertility can affect sperm morphology and physiology. Many studies on humans and animals suggest that both radiation and chemotherapy alter the sperm chromatin, inducing significant damage to sperm DNA, and decrease the level of protamination, thereby altering DNA compaction. Spermatozoa from cancer survivors are affected by chemotherapy even years after the end of treatment. We are exposed to various toxicants present in the environment (e.g., products of air pollution, pesticides, and plasticizers) whose impact on human male reproduction has not yet been established. This chapter aims to update our knowledge on how the sperm chromatin structure is modified by external agents and to describe the different strategies available to better study this complex structure in infertile men. Â© 2014 Springer Science+Business Media New York.","","","RefMan","","","","","","","","","" "Unknown","Unknown","Unknown","Unknown","","","2011","Oyarzun, M. P., Li, A. Y., Figueroa, C. C.","High levels of insecticide resistance in introduced horn fly (Diptera: Muscidae) populations and implications for management","Journal of economic entomology","104(1):258-65","773ce9c8-93ad-41d2-8d63-10ffd9167d42","","The horn fly, Haematobia irritans (L.) (Diptera: Muscidae), was introduced to Chile in the beginning of the 1990s. Since its introduction, farmers have controlled this pest almost exclusively with insecticides. To understand the consequences of different control strategies on the development of insecticide resistance and their persistence, a field survey was conducted at eight farms in the south of Chile to characterize insecticide resistance in field populations and resistance mechanisms. Horn fly samples were assayed to determine levels of resistance to pyrethroids and diazinon, genotyped for kdr and HialphaE7 mutations, and tested for general esterase activity. All field populations, including ones that were not treated with insecticides for the past 5 yr, showed high levels of cypermethrin resistance and high frequencies of the kdr mutation. None of the fly populations demonstrated resistance to diazinon and the HialphaE7 mutation was not detected in any of the fly samples. Esterase activities in all populations were comparable to those found in the susceptible reference strain. The findings of high frequencies of homozygous resistant and heterozygous individuals both in insecticide treated horn fly populations and in the untreated fly populations suggests complex interactions among field populations of the horn fly in Chile.","","","RefMan","","","","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2003","Pesando, D., Huitorel, P., Dolcini, V., Angelini, C., Guidetti, P., Falugi, C.","Biological targets of neurotoxic pesticides analysed by alteration of developmental events in the Mediterranean sea urchin, Paracentrotus lividus","Marine environmental research","55(1):39-57","afeaf29a-a447-421a-8a03-7c0619633fe8","","Biological effects of neurotoxic insecticides widely used for agricultural purposes were studied using the early development of the Mediterranean sea urchin Paracentrotus lividus as a model. These compounds, dispersed as aerosols or powders in agricultural regions near to the coast, may affect the health of organisms in the marine environment. The biological effects of Basudin (an organophosphate compound containing 20% Diazinon), Diazinon (Dzn, a thionophosphate), Carbaryl and Pirimicarb (carbamates) on the early phases of sea urchin development were thus investigated. Morphological, biochemical, histochemical and immuno histochemical analyses were performed both during embryo and larval development. For the morphological effects on fertilisation and first cleavages, the effective concentration of insecticides was found to be 10(-4) M, while for further stages concentrations between 10(-5) and 10(-7) M were effective: 10(-3) M of any of these insecticides totally arrested development. During embryonic development, the treatment with organophosphates slowed the rate of early mitotic cycles down, affected nuclear and cytoskeletal status as well as DNA synthesis. From the gastrulation stage onwards, the main effects were exerted on the rate of primary mesenchyme cells migration, larval size, perioral arm length, and acetylcholinesterase activity distribution, thus deregulating the cholinergic system, which modulates cell-to-cell communication mediated by the signal molecule acetylcholine.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2005","Pina-Guzman, B., Solis-Heredia, M. J., Quintanilla-Vega, B.","Diazinon alters sperm chromatin structure in mice by phosphorylating nuclear protamines","Toxicology and applied pharmacology","202(2):189-98","5b463846-605c-466c-8d25-155a21090487","","Organophosphorus (OP) pesticides, widely used in agriculture and pest control, are associated with male reproductive effects, including sperm chromatin alterations, but the mechanisms underlying these effects are unknown. The main toxic action of OP is related to phosphorylation of proteins. Chemical alterations in sperm nuclear proteins (protamines), which pack DNA during the last steps of spermatogenesis, contribute to male reproductive toxicity. Therefore, in the present study, we tested the ability of diazinon (DZN), an OP compound, to alter sperm chromatin by phosphorylating nuclear protamines. Mice were injected with a single dose of DZN (8.12 mg/kg, i.p.), and killed 8 and 15 days after treatment. Quality of sperm from epididymis and vas deferens was evaluated through standard methods and chromatin condensation by flow cytometry (DNA Fragmented Index parameters: DFI and DFI%) and fluorescence microscopy using chromomycin-A(3) (CMA(3)). Increases in DFI (15%), DFI% (4.5-fold), and CMA(3) (2-fold) were observed only at 8 days post-treatment, indicating an alteration in sperm chromatin condensation and DNA damage during late spermatid differentiation. In addition, an increase of phosphorous content (approximately 50%) in protamines, especially in the phosphoserine content (approximately 73%), was found at 8 days post-treatment. Sperm viability, motility, and morphology showed significant alterations at this time. These data strongly suggest that spermatozoa exposed during the late steps of maturation were the targets of DZN exposure. The correlation observed between the phosphorous content in nuclear protamines with DFI%, DFI, and CMA(3) provides evidence that phosphorylation of nuclear

protamines is involved in the OP effects on sperm chromatin.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2007","Povey, A. C., Jury, F., Dippnall, W. M., Smith, A. E., Thomson, S., Mackness, B., Mackness, M., Durrington, P., Cherry, N. M.","GST, CYP and PON1 polymorphisms in farmers attributing ill health to organophosphate-containing sheep dip","","12(2):188-202","48640d1e-e8a1-4903-a4ad-4b4ff5eb748d","","Previously we reported that in sheep dippers exposed to organophosphates the frequency of paraoxonase (PON1) polymorphisms differed between those with or without self-reported ill health. We have now examined whether polymorphisms in other genes involved in xenobiotic metabolism alter disease risk in this population. There were elevated but non-significant risks associated with the CYP2D6 WT genotype (odds ratio (OR) 1.47, 95% CI 0.83-2.60), or a GSTP1*B or *C allele (OR 1.37, 95% CI 0.88-2.01) or being GSTM1*2/GSTT1*2 homozygous (OR 1.61, 95% CI 0.74-3.48). Similar results were generally obtained after the exclusion of subjects to obtain a more homogenous case-referent population: for double null GSTM1 and GSTT1 homozygotes the OR was 2.06 (95% CI 0.85-2.04). In those also likely to have been exposed to diazinon, risks associated with a GSTP1*B or *C allele (OR 1.82, 95% CI 0.92-3.63) or a GSTM1*2/GSTT1*2 homozygous (OR 2.60, 95% CI 0.72-10.42) were elevated but not to a significant extent. Risk associated with PON1 genotype and phenotype varied with CYP2D6 and GSTP1 genotype but not consistently with a priori hypotheses. Further work is necessary to delineate more clearly pathways of organophosphate activation and non-PON1 pathways of detoxification and to confirm whether CYP and GST polymorphisms alter disease risk in populations exposed to organophosphates.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2013","Razavi, B. M., Hosseinzadeh, H., Movassaghi, A. R., Imenshahidi, M., Abnous, K.","Protective effect of crocin on diazinon induced cardiotoxicity in rats in subchronic exposure","Chemico-biological interactions","203(3):547-55","3f6899dc-9e1b-4155-a8f1-4c0641c59556","","This study was designed to evaluate the effectiveness of crocin, main component of Crocus sativus L. (Saffron) against subchronic diazinon (DZN) induced cardiotoxicity in rats. METHODS: Rats were divided into 7 groups; control (corn oil, gavage), DZN (15 mg/kg/day, gavage,), crocin (12.5, 25 or 50 mg/kg/day, i.p) plus DZN, vitamin E (200 IU/kg, i.p, three times per week) plus DZN and crocin (50 mg/kg/day, i.p) groups. Treatments were continued for 4 weeks. Creatine phosphokinase MB (CK-MB), malondealdehyde (MDA) and glutathione (GSH) levels were evaluated in heart tissue at the end of treatments. Levels of apoptotic proteins (Bax, Bcl2, caspase 3) and cytosolic cytochrome c were analyzed by Western blotting. Transcript levels of Bax and Bcl2 were also determined using qRT PCR. RESULTS: DZN induced histophatological damages and elevated the level of cardiac marker CK-MB. These effects were associated with increased MDA level, lower level of reduced GSH and induction of apoptosis through elevation of Bax/Bcl2 ratio (both protein and mRNA levels), cytochrome c release to the cytosol and activation caspase 3 in cardiac tissue. Crocin (25 and 50 mg/kg) or vitamin E improved histopathological damages, decreased MDA and CK-MB, increased GSH content and attenuated the increase of Bax/Bcl2 ratio, activation of caspase 3 and release of cytochrome c to the cytosol induced by DZN. In summary, DZN induced mitochondrial-mediated apoptosis in heart tissue of rat following subchronic exposure. Crocin, as an antioxidant, showed protective effects against DZN cardiotoxicity by reducing lipid peroxidation and alleviating apoptosis.","","","RefMan","","","","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2001","Sabourault, C., Guzov, V. M., Koener, J. F., Claudianos, C., Plapp, F. W., Jr., Feyereisen, R.","Overproduction of a P450 that metabolizes diazinon is linked to a loss-of-function in the chromosome 2 ali-esterase (MdalphaE7) gene in resistant house flies","Insect molecular biology","10(6):609-18","eb6dfe7c-eb45-4731-a814-cc43d543508f","","Up-regulation of detoxifying enzymes in insecticide-resistant strains of the house fly is a common mechanism for metabolic resistance. However, the molecular basis of this increased insecticide metabolism is not well understood. In the multiresistant Rutgers strain, several cytochromes P450 and glutathione S-transferases are constitutively overexpressed at the transcriptional level. Overexpression is the result of trans-regulation, and a regulatory gene has been located on chromosome 2. A Gly137 to Asp point mutation in alphaE7 esterase gene, leading to the loss of carboxylesterase activity, has been associated with organophosphate resistance in the house fly and the sheep blowfly. We show here that purified recombinant CYP6A1 is able to detoxify diazinon with a high efficiency. We also show that either the Gly137 to Asp point mutation in alphaE7 esterase gene or a deletion at this locus confer resistance and overproduction of the CYP6A1 protein. Based on these findings, we propose it is the absence of the wild-type Gly137 allele of the alphaE7 gene that releases the transcriptional repression of genes coding for detoxification enzymes such as CYP6A1, thereby leading to metabolic resistance to diazinon.","","","RefMan","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2010","Sadri, S., Bahrami, F., Khazaei, M., Hashemi, M., Asgari, A.","Cannabinoid receptor agonist WIN-55,212-2 protects differentiated PC12 cells from organophosphorus-induced apoptosis","","29(2):201-208","33565cdc-27c4-4d4e-ad57-e9e3c22bed11","","Cannabinoid neuroprotection is usually greater in vivo than in neuronal cell culture systems. To the authors' knowledge, a good in vitro culture model for the neuroprotective effects of cannabinoids does not exist. Therefore, a 3-dimensional (3D) culture system was developed to investigate the neuroprotective effects of the cannabinoid receptor agonist WIN-55,212-2 on apoptosis of differentiated PC12 cells, caused by the organophosphorus compounds paraoxon and diazinon. Cells pretreated with WIN-55,212-2 were exposed to a proapoptotic concentration of paraoxon and diazinon. TUNEL was used to detect apoptosis, and neurite length was assessed by morphometry. Both paraoxon and diazinon induced apoptosis, although the latter was more potent. WIN-55,212-2 also protected cells from neurite retraction and DNA fragmentation induced by the OPs. The results suggest that WIN-55,212-2 protects PC12 cells cultured under 3D conditions from organophosphorus-induced apoptosis. This 3D culture system may prove to be a useful tool for investigating the neuroprotective effects of cannabinoids. Â© The Author(s) 2010.","","","RefMan","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2008","Salazar-Arredondo, E., de Jesus Solis-Heredia, M., Rojas-Garcia, E., Hernandez-Ochoa, I., Quintanilla-Vega, B.","Sperm chromatin alteration and DNA damage by methyl-parathion, chlorpyrifos and diazinon and their oxon metabolites in human spermatozoa","Reproductive toxicology (Elmsford, N.Y.)","25(4):455-60","922b7252-b2c4-459a-958a-752772d5ebfa","","Extensive use of organophosphorous pesticides (OP) by young men represents a public health problem. Toxicity of OP mainly results in neurotoxicity due to their oxygen analogues (oxons), formed during the OP oxidative activation. OP alter semen quality and sperm chromatin and DNA at different stages of spermatogenesis. Oxons are more toxic than the parent

compounds; however, their toxicity to spermatogenic cells has not been reported. We evaluated sperm DNA damage by several OP compounds and their oxons in human spermatozoa from healthy volunteers incubated with 50-750 microM of methyl-parathion (MePA), methyl-paraoxon (MePO), chlorpyrifos (CPF), chlorpyrifos-oxon (CPO), diazinon (DZN) or diazoxon (DZO). All concentrations were not cytotoxic (evaluated by eosin-Y exclusion), except 750 microM MePO. Oxons were 15% to 10 times more toxic to sperm DNA (evaluated by the SCSA parameter, %DFI) than their corresponding parent compounds, at the following order: MePO>CPO=MePA>CPF>DZO>DZN, suggesting that oxon metabolites participate in OP sperm genotoxicity.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Sarabia, L., Maurer, I., Bustos-Obregon, E.","Melatonin prevents damage elicited by the organophosphorous pesticide diazinon on mouse sperm DNA","Ecotoxicology and environmental safety","72(2):663-8","4c661a4d-faac-4f1d-8bd5-150bf6783ab2","","Toxic effects of pesticides are commonly associated with DNA damage. To evaluate the effect of the organophosphate diazinon on sperm DNA and to test whether melatonin could prevent this damage, male mice were intraperitoneally treated with melatonin, diazinon (1/3 or 2/3 LD50) or both; cauda epididymal spermatozoa were obtained on days 1 and 32 postinjection and tested for DNA alterations. On day 1, sperm from diazinon-treated mice showed augmented DNA breakages and reduced chromatin packaging, whilst DNA damage increased only in the diazinon 2/3 LD50 group. Micronucleus test of bone marrow cells demonstrated somatic cell chromosomal damage in both diazinon-treated groups. Pretreatment with melatonin before diazinon acute administration improved all parameters studied on day 1 pi. The organophosphorous pesticide diazinon is a dose-dependent testicular toxicant that alters the sperm DNA structure; melatonin is able to prevent this damage.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2009","Sarabia, L., Maurer, I., Bustos-Obregon, E.","Melatonin prevents damage elicited by the organophosphorous pesticide diazinon on the mouse testis","Ecotoxicology and environmental safety","72(3):938-42","87bd0500-c124-470f-914b-34dd87277d98","","Organophosphates like O,O-diethyl O-2-isopropyl-6-methyl pyrimidinyl-4-g-1-phosphorothioate (diazinon) are pesticides used worldwide, which can affect both animals and man even after a single exposure. Whereas their toxicity is due to acetylcholinesterase inhibition, their secondary toxic effects have been related to free oxygen radicals. This study evaluates the effects of a single dose of diazinon and melatonin-a powerful antioxidant-on plasmatic acetylcholinesterase activity and testis histopathology in adult mice 1 and 32 days post-treatment. Diazinon diminished the plasma acetylcholinesterase activity on day 1 post-treatment, although testosterone levels remained unaffected. Morphometrical analysis showed a decrease in seminiferous epithelium height (days 1 and 32), whereas an increase in testicular superoxide dismutase (SOD) activity was detected (day 32). Melatonin pretreatment prevented every alteration induced by diazinon, except the diminution of acetylcholinesterase plasmatic activity. Testicular damage might be due to elevated concentrations of free oxygen radicals released upon diazinon exposure, inducing alterations in the DNA and promoting local apoptosis; however, antioxidant pretreatment with melatonin prevents or diminishes this damage.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Saulsbury, M. D., Heyliger, S., Li, F., Parker-Johnson, K. T. A.","Knock-down of base excision repair genes increases susceptibility to organophospate pesticide toxicity","","73(8)","c51fb2a6-ade9-4e30-

9d71-f28de217e575","","Organophosphates are chemicals that inhibit cholinesterases and are employed widely as pesticides. Concerns are increasing regarding the relative safety of these chemicals to the environment. Recent studies suggest organophosphate exposure is associated with increased expression of fragile sites and DNA damage at concentrations that are not associated with cholinesterase inhibition. Chronic exposure to the organophosphate has been associated with high incidences of prostate cancer in farm workers as well as leukemia and non-Hodgkin lymphoma in adults and children. Moreover, a higher degree of DNA damage has been reported in pesticide applicators that have polymorphisms in the base excision repair genes XRCC1 and OGG1. Our laboratory reports that cells deficient in BER enzymes APE1 and OGG1 exhibit a higher cytotoxicity when exposed, in a dose-dependent manner, to organophosphates Chlorpyrifos, Chlorpyrifos-oxon and Isofenphos. However, it should be noted that other organophosphates such as Diazinon and Dichlorvos had very little effects on cellular viability within the APE1 and OGG1 deficient cells. It should be noted that Chlorpyrifos, Chlorpyrifos-oxon and Isofenphos also produce significant oxidative stress in cells. Our data is consistent with previous studies which report a higher degree of DNA damage has been reported in pesticide applicators that have polymorphisms in the base excision repair genes XRCC1 and OGG1. Moreover, our data further suggests that only certain organophosphates, particularly those that induce oxidative stress, may be responsible for toxicity in APE1 and OGG1 deficient cells.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2003","Scott, J. G., Zhang, L.","The house fly aliesterase gene (MdalphaE7) is not associated with insecticide resistance or P450 expression in three strains of house fly","Insect biochemistry and molecular biology","33(2):139-44","8cb94257-83ec-40fb-96ec-12bb726a7d81","","It was recently proposed that a mutation (G137D) in the MdalphaE7 gene was responsible for increasing transcription of a P450 (CYP6A1) resulting in resistance to diazinon. To examine if MdalphaE7 had a role in resistance in other strains we sequenced a fragment (approximately 700 bp) of the MdalphaE7 gene from individual flies of two insecticide susceptible and three insecticide resistant (due to increased monooxygenase-mediated detoxification) strains. Five unique alleles were discovered. While all of the susceptible strains had Gly137, so did the resistant LPR and NG98 strains. Of the two alleles in the YPER strain one had the G137D substitution and the other did not. Based on the lack of correlation between the presence of the 'mutant' MdalphaE7 and resistance (or P450 levels), we conclude that the G137D mutation in MdalphaE7 is not involved in transcriptional control of the P450s involved in resistance in the LPR, NG98 or YPER strains. The relationship between MdalphaE7 alleles and insecticide resistance is discussed in light of these findings.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2015","Shadboorestan, A., Shokrzadeh, M., Ahangar, N., Abdollahi, M., Omidi, M., Payam, S. S.","The chemoprotective effects of L-carnitine against genotoxicity induced by diazinon in rat blood lymphocyte","Toxicology and industrial health","31(12):1334-40","1915cc73-a962-458c-831c-0c2c72737b78","","The purpose of this study was to assess the preventive effects of L-carnitine (LC) against DNA damage induced by diazinon (DZN) in rat blood lymphocytes. Animals were concurrently administered intraperitoneally with DZN in proper solvent (20 mg/kg body weight (b.w.)) and LC at three different doses (50, 100, and 150 mg/kg b.w.) for 30 consecutive days. The positive control group received DZN at

the same dose without LC. Twenty-four hour after last injection, 0.5 ml blood of each rat was received and cultured in culture medium for 44 h. The lymphocyte cultures were mitogenically stimulated with cytochalasin B for the evaluation of the number of micronuclei (MNs) in cytokinesis-blocked binucleated cells. Incubation of lymphocytes with DZN induced additional genotoxicity and was shown by increase in MNs frequency in rat lymphocytes. LC at all doses had a protective effect and significantly reduced the MNs frequency in cultured lymphocytes ($p < 0.0001$-$p < 0.05$). The maximum effect was observed at 150 mg/kg that reduced the frequency of MN from 12.78 +/- 0.24% for DZN group to 5.61 +/- 0.17%. Our study revealed that LC has a potent antigenotoxic effect against DZN-induced toxicity in rats, which may be due to the scavenging of free radicals and increased antioxidant status. Since LC is a natural compound and is being safe, it is recommended as a daily supplement for body defense against side effects induced by chemical hazardous agents.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Shokrzadeh, M., Ahangar, N., Abdollahi, M., Shadboorestan, A., Omidi, M., Payam, S. S.","Potential chemoprotective effects of selenium on diazinon-induced DNA damage in rat peripheral blood lymphocyte","Human & experimental toxicology","32(7):759-65","1d168ef1-53ae-46cc-989b-f93fac16fc55","","The purpose of this study was to investigate the protective effects of selenium (Se) against genotoxicity induced by diazinon (DZN) in rat peripheral blood lymphocytes by micronucleus (MN) test. Animals were concurrently administered intraperitoneally with DZN in proper solvent (20 mg/kg body weight (b.w.)) and Se at three different doses (0.5, 1, and 2 mg/kg b.w.) for 30 consecutive days. The positive control group received DZN at the same dose without Se. After 24 h of last injection, 0.5 ml blood of each rat was received and cultured in culture medium for 44 h. The lymphocyte cultures were mitogenically stimulated with cytochalasin B to allow the evaluation of number of MNs in cytokinesis-blocked binucleated cells. Incubation of lymphocytes with DZN induced additional genotoxicity and is shown by increase in MNs frequency in human lymphocytes. Se at low dose of 0.5 mg/kg had a maximum effect and significantly reduced the MNs frequency in cultured lymphocytes ($p < 0.0001$) that reduced the frequency of MN from 12.78 +/- 0.24% for DZN group to 4.40 +/- 0.36. The present study revealed that Se particularly at low doses has a potent antigenotoxic effect against DZN -induced toxicity in rats, which may be due to the scavenging of free radicals and increased antioxidant
status.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2015","Shokrzadeh, M., Ahmadi, A., Ramezaninejhad, S., Shadboorestan, A.","Hesperidin, a Citrus Bioflavonoid, Ameliorates Genotoxicity-induced by Diazinon in Human Blood Lymphocytes","","65(2):57-60","09a76c0d-7e16-4370-bbc3-e1bd2c6902bd","","Hesperidin (Hes), a natural bioflavonoid, is abundant in citrus fruit and has been reported to exert a wide range of pharmacological effects. Diazinon (DZN) can be mutagenic, or capable of inducing genetic damage, in human blood cells. The protective effect of Hes against DZN-induced micronucleus formation, an index of DNA damage, was investigated in human blood lymphocytes. Whole blood samples were collected from 5 volunteers and were incubated with different Hes concentrations for 3h. The samples were then incubated with 750Î¼M DZN for 24h. Subsequently, the blood samples were cultured with a mitogenic stimulant to evaluate micronucleus formation in cytokinesis-blocked binucleated lymphocytes. The incubation of blood samples with DZN induced additional genotoxicity in lymphocytes, and Hes pretreatment significantly reduced the micronucleus frequency ($p<0.01$-$p<0.001$).

Hes revealed a potent antigenotoxic effect against DZN-induced DNA damage, which may be due to free radical scavenging property. Since hesperidin is a natural compound and is considered safe, it can be used as a supplement to protect people exposed to chemical or environmental hazards.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Sirotkina, M., Efremenko, E. N.","Rhodococcus lactonase with organophosphate hydrolase (OPH) activity and His6-tagged OPH with lactonase activity: Evolutionary proximity of the enzymes and new possibilities in their application","","98(6):2647-2656","1ad72bed-ed63-467d-9056-b26c7c3e7821","","Decontamination of soils with complex pollution using natural strains of microorganisms is a matter of great importance. Here we report that oil-oxidizing bacteria Rhodococcus erythropolis AC-1514D and Rhodococcus ruber AC-1513D can degrade various organophosphorous pesticides (OP). Cell-mediated degradation of five different OP is apparently associated with the presence of N-acylhomoserine lactonase, which is pronouncedly similar (46-50 %) to the well-known enzyme organophosphate hydrolase (OPH), a hydrolysis catalyst for a wide variety of organophosphorous compounds. Additionally, we demonstrated the high lactonase activity of hexahistidine-tagged organophosphate hydrolase (His6-OPH) with respect to various N-acylhomoserine lactones, and we determined the catalytic constants of His6-OPH towards these compounds. These experimental data and theoretical analysis confirmed the hypothesis about the evolutionary proximity of OPH and lactonases. Using Rhodococcus cells, we carried out effective simultaneous biodegradation of pesticide paraoxon (88 mg/kg) and oil hydrocarbon hexadecane (6.3 g/kg) in the soil. Furthermore, the discovered high lactonase activity of His6-OPH offers new possibilities for developing an efficient strategy of combating resistant populations of Gram-negative bacterial cells. Â© 2013 Springer-Verlag.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2000","Smyth, K. A., Boyce, T. M., Russell, R. J., Oakeshott, J. G.","MCE activities and malathion resistances in field populations of the australian sheep blowfly (Lucilia cuprina)","Heredity","84 (Pt 1):63-72","8e7fd3e2-e7d0-4653-a871-e7d786a1e5db","","Malathion resistance has been shown to be the result of a single point mutation in the LcalphaE7 gene in four independently isolated chromosomes of Lucilia cuprina. The resultant amino acid substitution specifies high malathion carboxylesterase (MCE) activity. We have assayed MCE activities and resistance to malathion in three sets of field-derived samples, two sets of isogenic lines and five mass populations, and show that resistance to malathion in these samples is associated with high MCE activity in both sets of isogenic lines and four of the five mass populations. Additional mechanisms contributing to MCE activity or malathion resistance may be present in one of the mass populations. A second point mutation in LcalphaE7 is responsible for conferring diazinon resistance by encoding an increased organophosphate (OP) hydrolase activity. We also assayed diazinon resistances from the same three samples and show that diazinon and malathion resistances were in complete disequilibrium, with two exceptions. One exception involves the mass population with additional resistance mechanism(s) and the other involves three isogenic lines that are resistant to both insecticides. The molecular data for these lines suggest that they carry a duplication of the LcalphaE7 gene.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Sparling, D. W., Bickham, J., Cowman, D., Fellers, G. M., Lacher, T., Matson, C. W., McConnell, L.","In situ effects of pesticides on amphibians in the Sierra Nevada","","24(2):262-278","7997dfaf-d141-

4226-b6ee-9d6c6d9063c4","","For more than 20Â years, conservationists have agreed that amphibian populations around the world are declining. Results obtained through laboratory or mesocosm studies and measurement of contaminant concentrations in areas experiencing declines have supported a role of contaminants in these declines. The current study examines the effects of contaminant exposure to amphibians in situ in areas actually experiencing declines. Early larval Pseudacris regilla were translocated among Lassen Volcanic, Yosemite and Sequoia National Parks, California, USA and caged in wetlands in 2001 and 2002 until metamorphosis. Twenty contaminants were identified in tadpoles with an average of 1.3â€"5.9 (maximumÂ =Â 10) contaminants per animal. Sequoia National Park, which had the greatest variety and concentrations of contaminants in 2001, also had tadpoles that experienced the greatest mortality, slowest developmental rates and lowest cholinesterase activities. Yosemite and Sequoia tadpoles and metamorphs had greater genotoxicity than those in Lassen during 2001, as determined by flow cytometry. In 2001 tadpoles at Yosemite had a significantly higher rate of malformations, characterized as hemimelia (shortened femurs), than those at the other two parks but no significant differences were observed in 2002. Fewer differences in contaminant types and concentrations existed among parks during 2002 compared to 2001. In 2002 Sequoia tadpoles had higher mortality and slower developmental rates but there was no difference among parks in cholinesterase activities. Although concentrations of most contaminants were below known lethal concentrations, simultaneous exposure to multiple chemicals and other stressors may have resulted in lethal and sublethal effects.","","","RefMan","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2012","Temeyer, K. B., Brake, D. K., Schlechte, K. G.","Acetylcholinesterase of Haematobia irritans (Diptera: Muscidae): Baculovirus expression, biochemical properties, and organophosphate insensitivity of the G262A mutant","","49(3):589-594","d2424cec-7aab-474f-909b-15394000d9a7","","This study reports the baculovirus expression and biochemical characterization of recombinant acetylcholinesterase from Haematobia irritans (L.) (rHiAChE) and the effect of the previously described G262A mutation on enzyme activity and sensitivity to selected organophosphates. The rHiAChE was confirmed to be an insect AChE2-type enzyme with substrate preference for acetylthiocholine (Km 31.3 Î¼M) over butyrylthiocholine (K m 63.4 Î¼M) and inhibition at high substrate concentration. Enzyme activity was strongly inhibited by eserine (2.3 Ã- 10 -10 M), BW284c51 (3.4 Ã- 10-8 M), malaoxon (3.6 Ã- 10-8 M), and paraoxon (1.8 Ã- 10-7 M), and was less sensitive to the butyrylcholinesterase inhibitors ethopropazine (1.1 Ã- 10 -6M) and iso-OMPA (4.1 Ã- 10 -4 M). rHiAChE containing the G262A substitution exhibited decreased substrate affinity for both acetylthiocholine (Km 40.9 Î¼M) and butyrylthiocholine (Km 96.3 Î¼M), and exhibited eight-fold decreased sensitivity to paraoxon, and âˆ¼1.5- to 3-fold decreased sensitivity to other inhibitors. The biochemical kinetics are consistent with previously reported bioassay analysis, suggesting that the G262A mutation contributes to, but is not solely responsible for observed phenotypic resistance to diazinon or other organophosphates. Â© 2012 Entomological Society of America.","","","RefMan","","","","","","","","",""
"Unknown","Unknown","Unknown","Unknown","","","2008","Temeyer, K. B., Li, A. Y., Lohmeyer, K. H., Chen, A. C., Olafson, P. U., Sanson, D. W., Foil, L. D.","Acetylcholinesterase mutation in diazinon-resistant Haematobia irritans (L.) (Diptera: Muscidae)","","154(3-4):300-310","310c22a2-2b16-4dfe-8225-24a39ab38989","","Acetylcholinesterase (AChE) cDNA from individual field-collected

diazinon-resistant horn flies was amplified by RT-PCR. Sequencing of the amplification products revealed that 8/12 of the diazinon-resistant horn flies contained a point mutation previously associated with resistance to organophosphates in house flies and Drosophila, strongly suggesting that this cDNA encodes the AChE that is the target site for organophosphate (OP) pesticide. The point mutation (G262A) resulted in a shift from glycine to alanine in the mature HiAChE amino acid sequence at position 262. Allele-specific PCR and RLFP assays were developed to diagnose the presence or absence of the G262A mutation in individual flies. Use of the allele-specific assays each demonstrated the presence of the G262A mutation in 10 of 12 individual field-collected flies, demonstrating higher sensitivity than direct sequencing of RT-PCR amplification products. The G262A mutation was found in additional fly populations previously characterized as OP-resistant, further supporting that this AChE is the target site for OP pesticide. The allele-specific assay is a useful tool for quantitative assay of the resistance allele in horn fly populations.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2008","Timofeeva, O. A., Roegge, C. S., Seidler, F. J., Slotkin, T. A., Levin, E. D.","Persistent cognitive alterations in rats after early postnatal exposure to low doses of the organophosphate pesticide, diazinon","Neurotoxicology and teratology","30(1):38-45","3ab0b69d-2b4d-4b1c-90ec-74c2b9d0fd0c","","BACKGROUND: Developmental neurotoxicity of organophosphorous insecticides (OPs) involves multiple mechanisms in addition to cholinesterase inhibition. We have found persisting effects of developmental chlorpyrifos (CPF) and diazinon (DZN) on cholinergic and serotonergic neurotransmitter systems and gene expression as well as behavioral function. Both molecular/neurochemical and behavioral effects of developmental OP exposure have been seen at doses below those which cause appreciable cholinesterase inhibition. OBJECTIVES: We sought to determine if developmental DZN exposure at doses which do not produce significant acetylcholinesterase inhibition cause persisting cognitive deficits. METHODS: Rats were exposed to DZN on postnatal days 1-4 at doses (0.5 and 2 mg/kg/d) that span the threshold for cholinesterase inhibition. They were later examined with a cognitive battery tests similar to that used with CPF. RESULTS: In the T-maze DZN caused significant hyperactivity in the initial trials of the session, but not later. In a longer assessment of locomotor activity no DZN-induced changes were seen over a 1-hour session. Prepulse inhibition was reduced by DZN exposure selectively in males vs. females; DZN eliminated the sex difference present in controls. In the radial maze, the lower but not higher DZN dose significantly impaired spatial learning. This type of nonmonotonic dose-effect function has previously been seen with CPF as well. The lower dose DZN group also showed significantly greater sensitivity to the memory-impairing effects of scopolamine a muscarinic acetylcholine antagonist. CONCLUSIONS: Neonatal DZN exposure below the threshold for appreciable cholinesterase inhibition caused persisting neurocognitive deficits in adulthood. The addition of some inhibition of AChE with a higher dose reversed the cognitive impairment. This non-monotonic dose-effect function has also been seen with neurochemical effects. Some of the DZN effects on cognition resemble those seen earlier for CPF, some differ. Our data suggest that DZN and CPF affect transmitter systems supporting memory function, differently, implying participation of mechanisms other than their common inhibition of cholinesterase.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2007","Tisch, M., Faulde, M., Maier, H.","Genotoxic effects of insecticides in current use on mucosal epithelial cells from

human tonsil tissue","","55(SUPPL. 1):e15-e22","48a2919e-70f8-4806-a728-4cf4bc711bba","","Vector control is of critical medical importance in disease prevention, as reflected in sections 17 and 18 of the German Protection Against Infection Act. In the past, a large number of biocides were found to be hazardous to human health and were banned from the market, subsequently being replaced by new active ingredients and galenic forms. Many of these new insecticides are available in spray or nebuliser form. Whether these preparations have genotoxic effects on mucosal epithelial cells of the upper aerodigestive tract has thus far not been investigated. We used the comet assay, as a well-established genotoxicity test, to investigate whether malathion, diazinon, pyridostigmine bromide, piperonyl butoxide, silafluofen, and fipronil had genotoxic effects on tonsil specimens taken from 85 patients. All substances tested proved to have a strong genotoxic effect on mucosal epithelial cells taken from human tonsil tissue. We found clear differences between substance groups. Sufficient doses of a wide range of insecticides are indispensable in many areas of human life, especially for the prevention of diseases. Depending on the method of application, however, ingestion or inhalation of these substances can damage mucosal epithelial cells of the upper aerodigestive tract. Further epidemiological studies should be undertaken to investigate whether this involves potential health hazards in at-risk populations. . Â© Springer Medizin Verlag 2007.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2002","Tisch, M., Schmezer, P., Faulde, M., Groh, A., Maier, H.","Genotoxicity studies on permethrin, DEET and diazinon in primary human nasal mucosal cells","European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery","259(3):150-3","ded48bdb-e1e0-4a62-ab2a-354445250ca8","","Possible genotoxic effects exerted by three widely used pesticides, permethrin, N,N-diethyl-m-toluamide (DEET) and diazinon, in primary human nasal mucosal cells were investigated. Primary nasal mucosa cells were prepared from tissue biopsies taken from 21 patients who underwent nasal surgery. Cells were exposed to 0.5-1.0 mM concentrations of permethrin, DEET and diazinon for 60 min. Genotoxic effects were detected by the alkaline microgel electrophoresis assay (""comet assay""). Within the concentration range, no significant cytotoxic effects were observed, but all three tested pesticides showed a significant genotoxic response that was concentration dependent. More pronounced genotoxic effects were observed in mucosal cells from the middle turbinate than in the inferior turbinate. The results provide some evidence for the potential carcinogenicity of these agents to human nasal mucosal cells. This should be further investigated.","","","RefMan","","","","","","","","","","Unknown","Unknown","Unknown","Unknown","","","2006","Tope, A., Bebe, F. N., Panemangalore, M.","Micronuclei frequency in lymphocytes and antioxidants in the blood of traditional limited-resource farm workers exposed to pesticides","","41(6):843-853","ba990e8c-447b-463c-a3cb-52f9b0215982","","Chronic low-level exposure to synthetic pesticides is implicated in many health conditions that result from the induction of oxidative stress, including cytogenetic damage. The objective of this study was to assess the risk of genotoxicity using micronuclei (MN) formation in lymphocytes and to determine changes in blood antioxidants superoxide dismutase (SOD) in erythrocytes (E) and glutathione (GSH) in E and plasma (PL) in farm workers for six months during a growing season. Blood and urine samples were collected once a month for six months (June to November 2003) from farm workers (n = 15) and urban unexposed controls (n =

10). Lymphocytes from blood were separated by density gradient centrifugation using Histopaque and cultured using the standard technique. There was no significant difference in the cytokinesis blocked proliferation index (CBPI) of lymphocytes between the farm workers and the control group, but there was a 76% increase in average MN frequency in lymphocytes of the farm worker group (P â‰¤ 0.05). In addition, MN frequency peaked during August as compared to the other months and the controls (P â‰¤ 0.05). An 18% decline was observed in the activity of E-SOD in the farm worker group (P â‰¤ 0.05). GSH in E and PL were similar in both groups. These data suggest that the farm workers may be at a greater risk of developing genotoxicity due to continued exposure to pesticides, especially during the intensive growing season. Copyright Â© Taylor & Francis Group, LLC.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Tsitsimpikou, C., Tzatzarakis, M., Fragkiadaki, P., Kovatsi, L., Stivaktakis, P., Kalogeraki, A., Kouretas, D., Tsatsakis, A. M.","Histopathological lesions, oxidative stress and genotoxic effects in liver and kidneys following long term exposure of rabbits to diazinon and propoxur","","307:109-114","390ab56a-32b2-4fc5-9e1f-d52b5ef834d4","","Purpose: The aim of the present study was to investigate the effects of diazinon and propoxur on liver and kidneys, following long term exposure of rabbits. Methods: Ten New Zealand white female rabbits were used. The animals were divided into 5 groups, consisting of 2 animals each. Diazinon (groups 1 and 2) and propoxur (groups 3 and 4) were administered at 2 different doses, and group 5 served as the control group. Histopathological lesions in the liver and kidneys, oxidative stress and oxidative DNA damage were evaluated. Results: Both pesticides induced focal inflammation and fibrosis in the liver and kidneys. The low dose of propoxur induced a significant increase in total antioxidant capacity (TAC), with no difference in reduced glutathione (GSH), while the high dose of propoxur induced an increase in GSH with no change in TAC. For diazinon-exposed animals, the opposite findings were observed. Both diazinon and propoxur induced a statistically significant oxidative DNA damage in the liver and kidneys and a subsequent increase in telomerase activity in these tissues, possibly as a counteracting mechanism. Furthermore, systemic inflammation, as depicted by the dose-dependent increase in telomerase activity in peripheral blood mononuclear cells (PBMCs), was observed in propoxur treated animals. Conclusions: Histopathological lesions, oxidative stress and genotoxic effects were induced in liver and kidneys following long term exposure of rabbits to diazinon and propoxur. Â© 2012 Elsevier Ireland Ltd.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2010","Turgut, C., Ornek, H., Cutright, T. J.","Pesticide residues in dried table grapes from the Aegean region of Turkey","","167(1-4):143-149","b53e067e-6753-4191-860b-cbe240a5a944","","Dried grapes make the ideal low-calorie snack. The formation of gray mold during the drying of the grapes can severely decrease production. Pesticides and fungicides are applied to prevent losses due to pests and mold.Dried grapes from 99 farms in the Aegean region were sampled for pesticide residues. Of the 26 pesticides analyzed for, chlorpyrifos methyl, chlorpyrifos ethyl, deltamethrin, lambda-cyolathrin, dichlofluanid, iprodione, and procymidone were detected in the dried grapes. Only seven samples contained residues above the maximum residue limit. It is important to note that pesticide residues were only present in samples originating from vineyards using conventional farming practices. Â© Springer Science + Business Media B.V. 2009.","","","RefMan","","","","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2011","Ukpebor, J., Llabjani, V., Martin, F. L., Halsall, C. J.","Sublethal genotoxicity and cell alterations by organophosphorus pesticides in MCF-7 cells: Implications for environmentally relevant concentrations","","30(3):632-639","b06782f8-e5ea-4120-8af6-caa32e601cff","","Organophosphorus pesticide (OPP) toxicity is believed to be mediated through inhibition of acetylcholinesterase (AChE). Given their widespread distribution in aquatic systems and their ability to undergo chemical transformation, their environmental impacts at sublethal concentrations in nontarget organisms have become an important question. We conducted a number of mammalian-cell genotoxic and gene expression assays and examined cellular biochemical changes that followed low-dose exposure of MCF-7 cells to fenitrothion, diazinon, and the aqueous degradate of diazinon, 2-isopropyl-6-methyl-4-pyrimidinol (IMP). After exposure to the OPPs at low concentrations (10-12M to 10-8 M), greater than twofold elevations in micronucleus formation were noted in MCF-7 cell cultures that went on to exhibit greater than 75% clonogenic survival; these levels of chromosomal damage were comparable to those induced by 10-6 M benzo[a]pyrene, a known genotoxic agent. At this low concentration range, a fenitrothion-induced twofold elevation in B-cell leukemia/lymphoma-2 (BCL-2) and cytochrome P450 isoenzyme (CYP1A1) gene expressions was observed. Principal component analysis-linear discriminant analysis (PCA-LDA) of derived infrared (IR) spectra of vehicle control (nonexposed) and OPP-exposed cells highlighted that both fenitrothion and diazinon induced marked biochemical alterations in the lipid, protein, and DNA/RNA absorbance regions. Our findings demonstrate that the two OPP parent chemicals and IMP degradate can mediate a number of toxic effects or cellular alterations at very low concentrations. These are independent of just selective inhibition of AChE, with potential consequences for nontarget organisms exposed at environmentally relevant concentrations. Further assays on relevant aquatic organism cell lines are now recommended to understand the mechanistic low-dose toxicity of these chemicals present in aquatic systems. Environ. Toxicol. Chem. 2011; 30:632-639. Â© 2011 SETAC Copyright Â© 2011 SETAC.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","van Thriel, C.","Recent research in neurotoxicology","","10:135-137","45276eac-63c3-4b59-94f0-cbf83e0e2b0d","","Large projects are currently ongoing to establish in vitro systems for identification of com-pounds that induce neurotoxicity or developmental neurotoxicity (Hardelauf et al., 2011; Fri-mat et al., 2010). An example is the EU funded network ESNATS where human embryonic stem cells are differentiated to neuronal cells. This gives the opportunity to expose the differentiating stem cells to test chemicals during specific sensitive periods and analyze if the differentiation process is compromised. However, this is an ongoing project and it will take several years until the novel in vitro techniques can be integrated into routine toxicological testing. Current publications still include in vivo studies, for example possible neurotoxic effects of diesel exhaust in newborn mice (Tsukue et al., 2009), developmental neurotoxicity of acrylamide in rats (Takahashi et al., 2009) and oxidative stress in the cerebral cortex of rats after exposure to diphenyl ditelluride (Stangherlin et al., 2009). It remains currently difficult to predict, when it will be possible to replace conventional neurotoxicity in vivo studies by in vitro tests. The table gives an overview over recent studies in neurotoxicology or developmental neurotoxicology.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2013","Von Stackelberg, K.","A systematic review of carcinogenic outcomes and potential mechanisms from exposure to

2,4-D and MCPA in the environment","","2013","c422b0ef-2ee0-4200-845f-b60cda663f98","","Chlorophenoxy compounds, particularly 2,4-dichlorophenoxyacetic acid (2,4-D) and 4-chloro-2-methylphenoxy)acetic acid (MCPA), are amongst the most widely used herbicides in the United States for both agricultural and residential applications. Epidemiologic studies suggest that exposure to 2,4-D and MCPA may be associated with increased risk non-Hodgkins lymphoma (NHL), Hodgkin's disease (HD), leukemia, and soft-tissue sarcoma (STS). Toxicological studies in rodents show no evidence of carcinogenicity, and regulatory agencies worldwide consider chlorophenoxies as not likely to be carcinogenic or unclassifiable as to carcinogenicity. This systematic review assembles the available data to evaluate epidemiologic, toxicological, pharmacokinetic, exposure, and biomonitoring studies with respect to key cellular events noted in disease etiology and how those relate to hypothesized modes of action for these constituents to determine the plausibility of an association between exposure to environmentally relevant concentrations of 2,4-D and MCPA and lymphohematopoietic cancers. The combined evidence does not support a genotoxic mode of action. Although plausible hypotheses for other carcinogenic modes of action exist, a comparison of biomonitoring data to oral equivalent doses calculated from bioassay data shows that environmental exposures are not sufficient to support a causal relationship. Genetic polymorphisms exist that are known to increase the risk of developing NHL. The potential interaction between these polymorphisms and exposures to chlorophenoxy compounds, particularly in occupational settings, is largely unknown. Â© 2013 Katherine von Stackelberg.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2007","Wilkinson, D. A., Hulst, A. G., de Reuver, L. P., van Krimpen, S. H., van Baar, B. M.","The fate of the chemical warfare agent during DNA extraction","Journal of forensic sciences","52(6):1272-83","08fc9f07-ef9e-4f87-bbce-c5a682e5b7cc","","Forensic laboratories do not have the infrastructure to process or store contaminated DNA samples that have been recovered from a crime scene contaminated with chemical or biological warfare agents. Previous research has shown that DNA profiles can be recovered from blood exposed to several chemical warfare agents after the agent has been removed. The fate of four toxic agents, sulfur mustard, sodium 2-fluoroacetate, sarin, and diazinon, in a lysis buffer used in Promega DNA IQ extraction protocol was studied to determine if extraction would render the samples safe. Two independent analytical methods were used per agent, selected from GC-MS, 1H NMR, 19F NMR, (31)P NMR, or LC-ES MS. The methods were validated before use. Determinations were carried out in a semi-quantitative way, by direct comparison to standards. Agent levels in the elution buffer were found to be below the detectable limits for mustard, sarin, sodium 2-fluoroacetate or low (<0.02 mg/mL) for diazinon. Therefore, once extracted these DNA samples could be safely processed in a forensic laboratory.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2006","Willoughby, L., Chung, H., Lumb, C., Robin, C., Batterham, P., Daborn, P. J.","A comparison of Drosophila melanogaster detoxification gene induction responses for six insecticides, caffeine and phenobarbital","","36(12):934-942","d3a88f4d-4625-4a7f-9944-d952fb0c2f39","","Modifications of metabolic pathways are important in insecticide resistance evolution. Mutations leading to changes in expression levels or substrate specificities of cytochrome P450 (P450), glutathione-S-transferase (GST) and esterase genes have been linked to many cases of resistance with the responsible enzyme shown to utilize the insecticide as a substrate. Many studies show that the substrates of

enzymes are capable of inducing the expression of those enzymes. We investigated if this was the case for insecticides and the enzymes responsible for their metabolism. The induction responses for P450s, GSTs and esterases to six different insecticides were investigated using a custom designed microarray in Drosophila melanogaster. Even though these gene families can all contribute to insecticide resistance, their induction responses when exposed to insecticides are minimal. The insecticides spinosad, diazinon, nitenpyram, lufenuron and dicyclanil did not induce any P450, GST or esterase gene expression after a short exposure to high lethal concentrations of insecticide. DDT elicited the low-level induction of one GST and one P450. These results are in contrast to induction responses we observed for the natural plant compound caffeine and the barbituate drug phenobarbital, both of which highly induced a number of P450 and GST genes under the same short exposure regime. Our results indicate that, under the insecticide exposure conditions we used, constitutive over-expression of metabolic genes play more of a role in insect survival than induction of members of these gene families. Â© 2006 Elsevier Ltd. All rights reserved.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Xu, L., Wu, M., Han, Z.","Biochemical and molecular characterisation and cross-resistance in field and laboratory chlorpyrifos-resistant strains of Laodelphax striatellus (Hemiptera: Delphacidae) from eastern China","Pest management science","70(7):1118-29","20f164e4-2ab6-4265-be0d-cec13de0ff0f","","BACKGROUND: Laboratory selection is often employed in resistance mechanism studies because field-derived populations commonly do not have high enough resistance for such studies. In the present study, a field-collected Laodelphax striatellus population from eastern China was laboratory selected for chlorpyrifos resistance and susceptibility, and the developed strains, along with a field population, were studied for cross-resistance and resistance mechanisms at biochemical and molecular levels. RESULTS: A 158.58-fold chlorpyrifos-resistant strain (JH-chl) and a chlorpyrifos-susceptible strain (JHS) were established after laboratory selection of 25 generations. Cross-resistance to deltamethrin, diazinon, methomyl, carbosulfan, acephate and imidacloprid were detected in JH-chl and a field-collected strain (JHF). Synergism and enzyme activity data suggested potential involvement of P450s and esterases in JH-chl as well as AChE alteration. Furthermore, CYP6AY3v2, CYP306A2v2, CYP353D1v2 and LSCE36 genes were significantly overexpressed in JH-chl (6.87-12.14-fold). Feeding of dsRNAs reduced the expression of the four target genes (35.6-56.8%) and caused significant adult mortality (75.21-88.45%), implying resistance reduction. However, mechanism(s) conferring chlorpyrifos resistance in JHF were unclear. CONCLUSION: In contrast to previous reports, multiple overexpressed detoxification genes were potentially associated with chlorpyrifos resistance, as confirmed by RNAi feeding tests. Chlorpyrifos resistance exhibits cross-resistance with insecticides in the same and different classes.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Yamamoto, K., Ichinose, H., Aso, Y., Banno, Y., Kimura, M., Nakashima, T.","Molecular characterization of an insecticide-induced novel glutathione transferase in silkworm","","1810(4):420-426","12dafcc9-9d6f-4458-b686-e7e9f312d149","","Background: The glutathione transferase (GST) superfamily is involved in the detoxification of various xenobiotics. We have identified a GST mRNA that was induced in the fat bodies of a silkworm strain exhibiting diazinon resistance and have investigated the enzyme properties of this GST.

Methods: A soluble recombinant protein was overexpressed in Escherichia coli. Amino acid residues of interest were changed to alanine by site-directed mutagenesis. Results and conclusions: Phylogenetic analysis of the deduced amino acid sequence indicates that this GST belongs to an unclassified group previously reported in mosquitoes. This enzyme, named bmGSTu, has highly conserved amino acid residues, including Tyr7, Ser12 and Asn50. A recombinant bmGSTu was able to catalyze the biotranslation of glutathione with 1-chloro-2,4-dinitrobenzene, a synthetic substrate of GST. Kinetic analysis of bmGSTu mutants indicated that Tyr7, Ser12 and Asn50 are involved in enzyme function. General significance: These results support the hypothesis that bmGSTu may play a role in insecticide resistance in Bombyx mori. ","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2014","Zafiropoulos, A., Tsarouhas, K., Tsitsimpikou, C., Fragkiadaki, P., Germanakis, I., Tsardi, M., Maravgakis, G., Goutzourelas, N., Vasilaki, F., Kouretas, D., Hayes, A., Tsatsakis, A.","Cardiotoxicity in rabbits after a low-level exposure to diazinon, propoxur, and chlorpyrifos","Human & experimental toxicology","33(12):1241-52","cbb689e4-1dcc-4b90-8a85-0f8dc1193420","","Lethal cardiac complications leading to death and various arrhythmias have been reported after organophosphate and/or carbamate poisonings. The present study focuses on the long-term effects of repeated low-level exposure to diazinon, propoxur, and chlorpyrifos (CPF) on cardiac function in rabbits. The yearly based experimental scheme of exposure consisted of two oral administration periods, lasting 3 months and 1 month each, interrupted by an 8-month washout period (total duration 12 months). At the end of the experimental scheme, the rabbits underwent an echocardiographic evaluation under sedation, after which they were killed and the tissue and serum samples were collected. A mild localized cardiotoxic effect was established by echocardiography for the three pesticides tested. Severe histological alterations were identified, especially in the diazinon-treated animals in agreement with increased persistence of this pesticide established in the cardiac tissue. In addition, all pesticides tested increased the oxidative stress and oxidative modifications in the genomic DNA content of the cardiac tissues, each one following a distinct mechanism.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2007","Zeng, R. S., Wen, Z., Niu, G., Schuler, M. A., Berenbaum, M. R.","Allelochemical induction of cytochrome P450 monooxygenases and amelioration of xenobiotic toxicity in Helicoverpa zea","Journal of chemical ecology","33(3):449-61","ed791438-7ce1-405f-9193-2261af8d86da","","Polyphagous herbivores encounter allelochemicals as complex mixtures in their host plants, and the toxicity of an individual compound may be influenced by the chemical matrix in which it is encountered. Certain plant constituents may reduce toxicity of cooccurring compounds by inducing detoxification systems, including cytochrome P450s, which can metabolize a broad range of substances. The polyphagous corn earworm Helicoverpa zea encounters a diversity of plant allelochemicals in its many host plants and, as well, can encounter aflatoxins, mycotoxins produced by Aspergillus flavus and Aspergillus parasiticus that infect damaged grains. Dietary supplementation of each of three plant allelochemicals that are frequently (coumarin, COU), occasionally (indole-3-carbinol, 13C), or rarely (xanthotoxin, XAN) encountered by H. zea larvae substantially reduced the toxicity of aflatoxin B1 (AFB1) to H. zea. Compared to fourth instars on diets containing 1 microg/g AFB1 that failed to develop and pupate, fourth instars on diets containing I3C and XAN increased in mass by 216.1 and 700% after 6 days, and pupated at rates of 40

and 88%, respectively. Diets containing COU or XAN also significantly reduced the mortality rates of caterpillars exposed to the insecticides, diazinon and carbaryl. Diets containing COU and XAN increased CYP6B8 transcripts 2.6-fold; CYP321A1 transcripts increased 20.7, 8.3, and 10.6-fold in response to COU, I3C, and XAN, respectively. These results indicate that consumption of plant allelochemicals can ameliorate toxicity of natural and synthetic toxins encountered by insects, and they suggest that P450s induced by these allelochemicals contribute to detoxification of these chemicals in H. zea.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2011","Zhang, X., Wallace, A., Du, P., Baccarelli, A., Jafari, N., Lin, S., Hou, L.","Genome-wide study of DNA methylation alterations in response to pesticide exposure in in vitro","","71(8)","4337128f-d39b-4d75-ac8b-e64763fc2a7c","","Pesticides are widely used in the US and worldwide, and are pervasive in our environment. All pesticides sold in the US have passed the Environmental Protection Agency (EPA) screening procedures for carcinogenicity based on their genotoxicity and mutagenicity. However exposure to pesticides among pesticide applicators and manufacturing workers has repeatedly been shown to increase cancer risk, suggesting that pesticides may cause cancer via alternative mechanisms, such as epigenetic changes. The purpose of the present study is to examine whether exposure to organophosphate pesticides (OPs), a group of the most commonly used pesticides in the US, induces DNA methylation alterations in in-vitro. The K562 progenitor blood cell line was exposed to several OPs (i.e., chlorpyrifos, diazinon, fonofos, malathion, parathion, phorate, and terbufos) at different dosages and time periods. DNA was prepared from samples exposed to ethanol (control) and a range of pesticide concentrations similar to exposure levels experienced by the US licensed pesticide applicators. We conducted genomewide DNA methylation analysis using the Illumina Infinium HumanMethylation27 BeadChip that covers 27,578 individual promoter CpG sites in the entire genome. The relative level of methylation was calculated as the ratio of signal from a methylated probe relative to an unmethylated probe. Bayesian-adjusted t-tests were used to identify differentially methylated sites. A cut-off of False Discovery Rate (FDR)-adjusted p-value (q-value) < 0.05 and fold change > 2 was used to identify candidate CpG sites. We observed significant differences in genomewide DNA methylation patterns in relation to exposure to three pesticides (i.e., fonofos, parathion, and terbufos) that have been associated with cancers in human studies. Out of all genes with differentially methylated CpG site(s) for each of the three pesticides, we identified 712 genes (625 were hypermethylated and 87 were hypomethylated) overlapped for these three pesticides. Gene ontology analysis showed that these hyper- or hypo-methylated genes are implicated in carcinogenesis and related biological process, such as tumor protein p53 inducible protein 11 (TP53I11) (4.0-fold for fonofos, 4.7-fold for parathion, 3.1-fold for terbufos, respectively), growth arrest and DNA-damage-inducible gamma (GADD45G) (25.2-fold for fonofos, 23.1-fold for parathion, 31.2-fold for terbufos, respectively), and interleukin-1 receptor (IL1R1) (-2.2-fold for fonofos, -2.1-fold for parathion, -2.2 fold for terbufos, respectively). Our results provided direct experimental evidence that pesticides can modify DNA methylation in gene promoter CpG sites, which may play pathological role in cancer development. Further studies in other cell types and human samples are required before any firm conclusion could be reached on the significance of pesticide-induced methylation.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Zhang, X., Wallace, A. D., Du,

P., Kibbe, W. A., Jafari, N., Xie, H., Lin, S., Baccarelli, A., Soares, M. B., Hou, L.","DNA methylation alterations in response to pesticide exposure in vitro","","53(7):542-549","65b0b51d-3995-40e0-8ed4-205c79767d49","","Although pesticides are subject to extensive carcinogenicity testing before regulatory approval, pesticide exposure has repeatedly been associated with various cancers. This suggests that pesticides may cause cancer via nonmutagenicity mechanisms. The present study provides evidence to support the hypothesis that pesticide-induced cancer may be mediated in part by epigenetic mechanisms. We examined whether exposure to seven commonly used pesticides (i.e., fonofos, parathion, terbufos, chlorpyrifos, diazinon, malathion, and phorate) induces DNA methylation alterations in vitro. We conducted genome-wide DNA methylation analyses on DNA samples obtained from the human hematopoietic K562 cell line exposed to ethanol (control) and several organophosphate pesticides (OPs) using the Illumina Infinium HumanMethylation27 BeadChip. Bayesian-adjusted t-tests were used to identify differentially methylated gene promoter CpG sites. In this report, we present our results on three pesticides (fonofos, parathion, and terbufos) that clustered together based on principle component analysis and hierarchical clustering. These three pesticides induced similar methylation changes in the promoter regions of 712 genes, while also exhibiting their own OP-specific methylation alterations. Functional analysis of methylation changes specific to each OP, or common to all three OPs, revealed that differential methylation was associated with numerous genes that are involved in carcinogenesis-related processes. Our results provide experimental evidence that pesticides may modify gene promoter DNA methylation levels, suggesting that epigenetic mechanisms may contribute to pesticide-induced carcinogenesis. Further studies in other cell types and human samples are required, as well as determining the impact of these methylation changes on gene expression. Â© 2012 Wiley Periodicals, Inc.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Zhang, X., Wallace, A. D., Du, P., Lin, S., Baccarelli, A. A., Jiang, H., Jafari, N., Zheng, Y., Xie, H., Soares, M. B., Kibbe, W. A., Hou, L.","Genome-wide study of DNA methylation alterations in response to diazinon exposure in vitro","Environmental toxicology and pharmacology","34(3):959-68","acf15149-0ab4-41a4-9e90-75caca7a6117","","Pesticide exposure has repeatedly been associated with cancers. However, molecular mechanisms are largely undetermined. In this study, we examined whether exposure to diazinon, a common organophosphate that has been associated with cancers, could induce DNA methylation alterations. We conducted genome-wide DNA methylation analyses on DNA samples obtained from human hematopoietic K562 cell exposed to diazinon and ethanol using the Illumina Infinium HumanMethylation27 BeadChip. Bayesian-adjusted t-tests were used to identify differentially methylated gene promoter CpG sites. We identified 1069 CpG sites in 984 genes with significant methylation changes in diazinon-treated cells. Gene ontology analysis demonstrated that some genes are tumor suppressor genes, such as TP53INP1 (3.0-fold, q-value <0.001) and PTEN (2.6-fold, q-value <0.001), some genes are in cancer-related pathways, such as HDAC3 (2.2-fold, q-value=0.002), and some remain functionally unknown. Our results provided direct experimental evidence that diazinon may modify gene promoter DNA methylation levels, which may play a pathological role in cancer development.","","","RefMan","","","","","","","","","","
"Unknown","Unknown","Unknown","Unknown","","","2012","Zhang, Y., An, J., Ye, W., Yang, G., Qian, Z. G., Chen, H. F., Cui, L., Feng, Y.","Enhancing the promiscuous phosphotriesterase activity of a thermostable lactonase (GkaP) for the efficient

degradation of organophosphate pesticides","","78(18):6647-6655","8667c934-03dd-4b43-a0c8-30f90702625f","","The phosphotriesterase-like lactonase (PLL) enzymes in the amidohydrolase superfamily hydrolyze various lactones and exhibit latent phosphotriesterase activities. These enzymes serve as attractive templates for in vitro evolution of neurotoxic organophosphates (OPs) with hydrolytic capabilities that can be used as bioremediation tools. Here, a thermostable PLL from Geobacillus kaustophilus HTA426 (GkaP) was targeted for joint laboratory evolution with the aim of enhancing its catalytic efficiency against OP pesticides. By a combination of site saturation mutagenesis and whole-gene error-prone PCR approaches, several improved variants were isolated. The most active variant, 26A8C, accumulated eight amino acid substitutions and demonstrated a 232-fold improvement over the wild-type enzyme in reactivity (kcat/Km) for the OP pesticide ethyl-paraoxon. Concomitantly, this variant showed a 767-fold decrease in lactonase activity with Î´-decanolactone, imparting a specificity switch of 1.8 Ã- 105-fold. 26A8C also exhibited high hydrolytic activities (19- to 497-fold) for several OP pesticides, including parathion, diazinon, and chlorpyrifos. Analysis of the mutagenesis sites on the GkaP structure revealed that most mutations are located in loop 8, which determines substrate specificity in the amidohydrolase superfamily. Molecular dynamics simulation shed light on why 26A8C lost its native lactonase activity and improved the promiscuous phosphotriesterase activity. These results permit us to obtain further insights into the divergent evolution of promiscuous enzymes and suggest that laboratory evolution of GkaP may lead to potential biological solutions for the efficient decontamination of neurotoxic OP compounds. Â© 2012, American Society for Microbiology.","","","RefMan","","","","","","","","","","